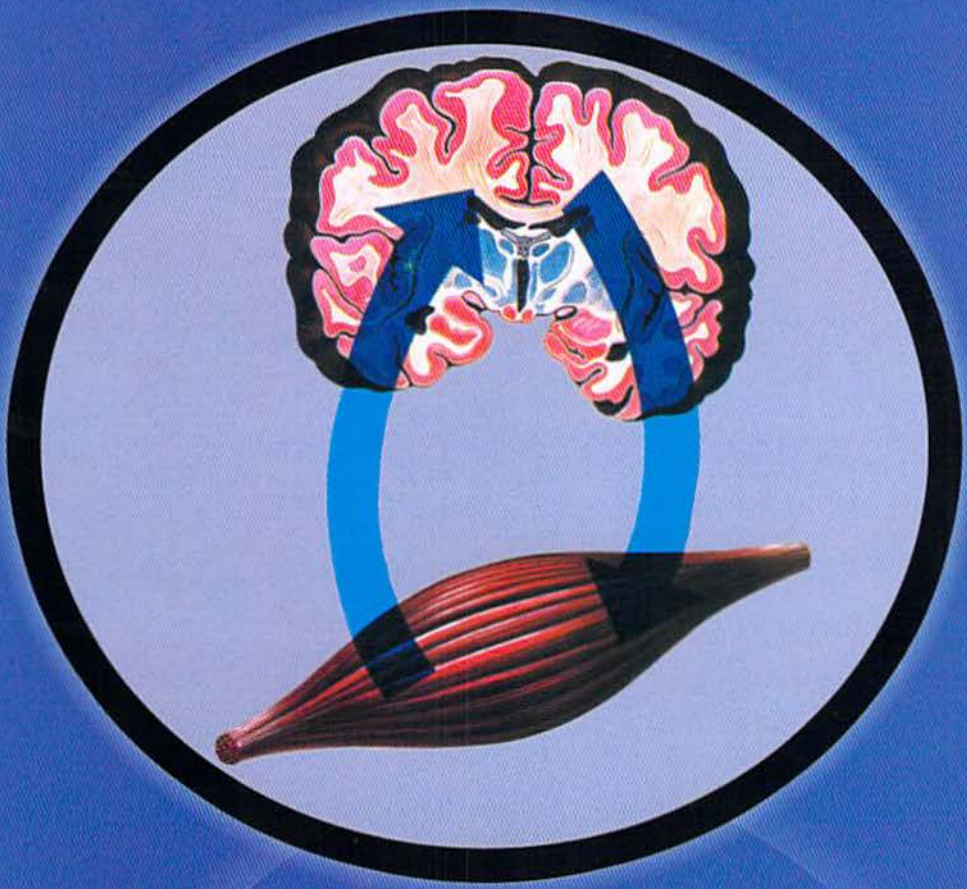
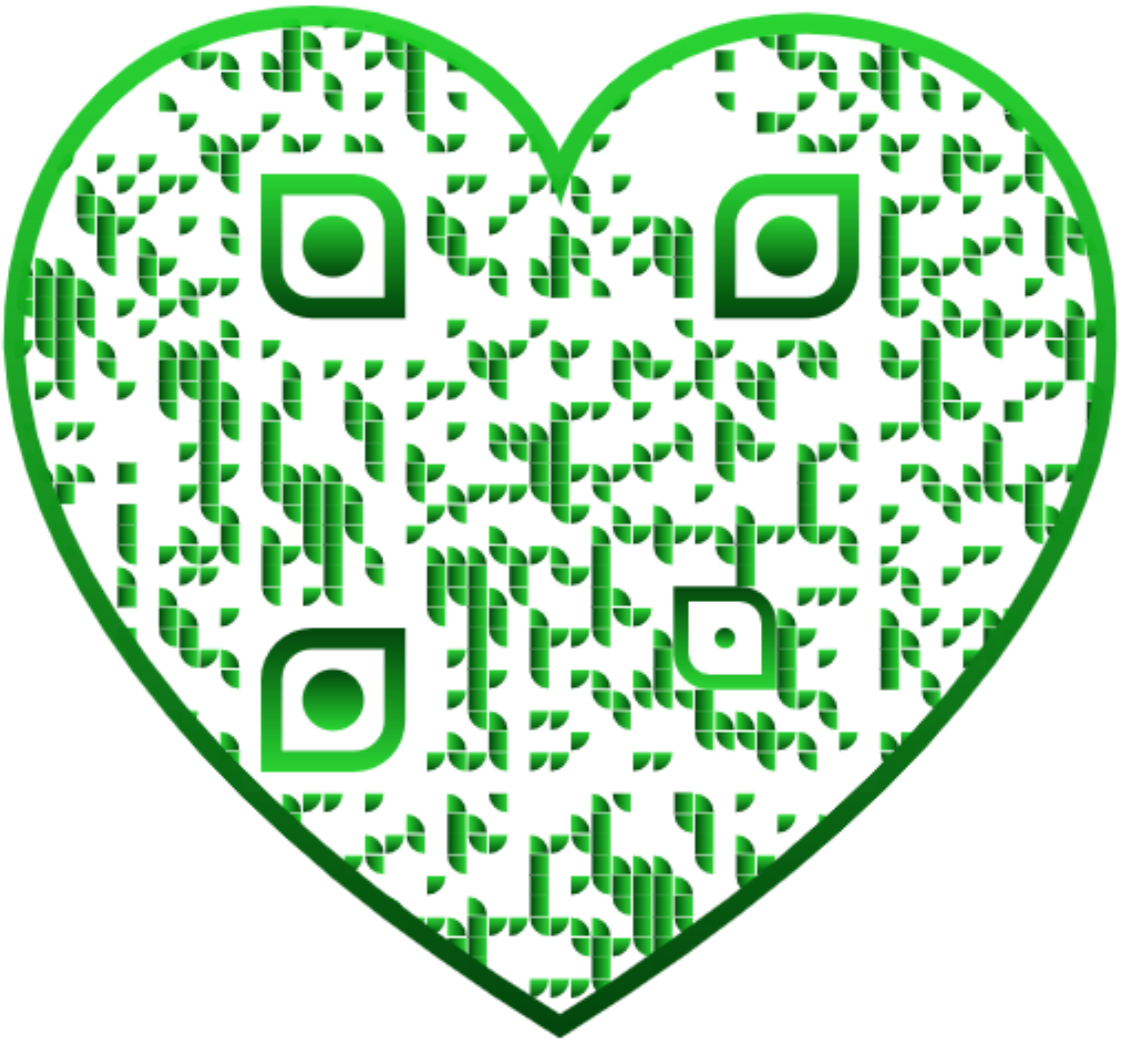
Human PHYSIOLOGY

for medical students



AUTONOMIC NERVOUS SYSTEM & NERVE AND MUSCLE

Magdi Sabry M.D.



HUMAN
PHYSIOLOGY
FOR MEDICAL STUDENTS

AUTONOMIC NERVOUS SYSTEM
&
NERVE AND MUSCLE

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DEDICATED TO

MY TEACHERS THROUGHOUT MY LIFE, *particularly the first 2 teachers, my late parents.*

MY FAITHFUL LATE WIFE, *the light that disappeared from life but is everlasting inside me.*

MY SONS, SHERIF, AMR AND ESSAM, AND THEIR WIVES, *their love gives me hope and interest in life and makes their happiness my chief goal.*

MY GRANDCHILDREN, AHMED, NOURHAN and SAMA SHERIF, YASMIN and MOHAMMED AMR, AND AYA and ALY ESSAM, *the beautiful young angels that have added a new kind of happiness to my life.*

PREFACE

With recent advances in the field of human physiology, it has become urgent to provide an up to date review on the subject.

This book is provided to help medical students in understanding modern human physiology. It presents the whole subject in a brief, comprehensive, and up to date form.

Great effort was done to perfect such a vast subject in an easily understandable expression and in a such reasonable bulk. It includes as much simplified and clear illustrations as possible,and to maintain simplicity, they have been presented in a diagrammatic form, photographs were greatly excluded.

The major part of my gratitude should be given to all who taught me, and to my late wife and sons who, patiently, supported me during preparation of this book.

Any suggestions, remarks or criticism will be greatly welcomed, heartily appreciated and very much considered.

I hope this book will be a real help to undergraduate medical students as well as to postgraduates and candidates of higher degrees, in the field of human physiology.

MAGDI SABRY, 1988

Second edition 1993

Third edition 1997

Fourth edition 2001

Preface to the fifth edition

This new edition is original both in shape and contents. All chapters have been extensively revised and updated. More figures and illustrations were introduced, and recent data were added elsewhere specially about the autonomic receptors and the mechanism of muscle contraction, and most subjects have been completely rewritten.

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SECTION I

AUTONOMIC NERVOUS SYSTEM

GENERAL FEATURES OF THE AUTONOMIC N.S.

Definition of the autonomic nervous system (A.N.S.)

The A.N.S. is a part of the nervous system that controls the involuntary functions in the body i.e. functions of the viscera, glands, heart and blood vessels (so it is also called the ***visceral or involuntary nervous system***). In contrast, the voluntary functions are controlled by a much larger part of the nervous system called the ***somatic N.S.*** (*soma = body*) which is commonly known as the ***central nervous system*** (or the ***C.N.S.***).

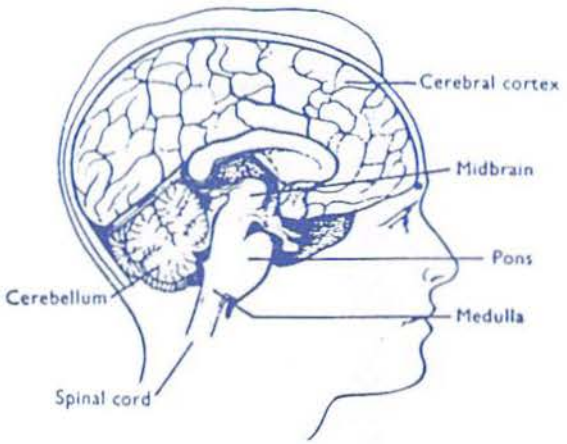


Figure 1 : Various parts of the human brain.

Functional anatomy of the nervous system

Anatomically, the nervous system is divided into 2 parts :

(A) Central nervous system : This is formed of the ***brain*** and ***spinal cord***.

(1) The brain : From above downwards, it consists of the following parts (figure 1) :

(a) ***The cerebral cortex*** : This is formed of ***2 cerebral hemispheres***, below which there are several important nuclei (***the thalamus, hypothalamus*** and ***basal ganglia***).

(b) ***The brain stem*** : This contains from above downwards, the ***midbrain, pons*** and ***medulla oblongata***.

(c) ***The cerebellum***.

(2) The spinal cord : This is formed of ***31 segments*** which are from above downwards, ***8 cervical, 12 thoracic, 5 lumbar, 5 sacral*** and ***one coccygeal segment*** (figure 2).

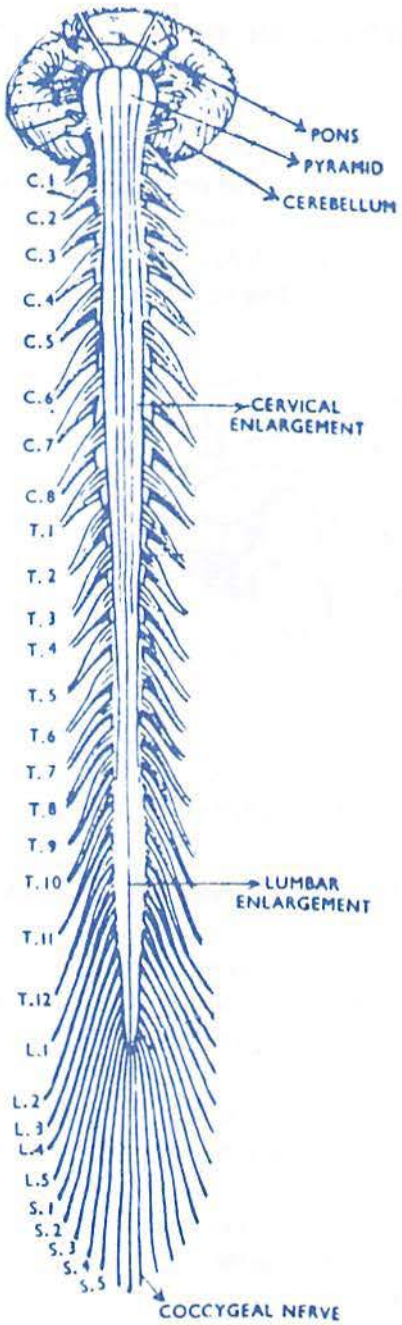


Figure 2 : The spinal cord.

(B) Peripheral nervous system : This consists of the peripheral nerves that arise from the central nervous system, and they include :

(1) ***The cranial nerves*** : These are ***12 pairs*** of nerves that arise mostly from the brain stem and supply various structures in the head.

(2) ***The spinal nerves*** **:** These are ***31 pairs*** of nerves that arise from the spinal cord (one from each segment) and supply various structures in the rest of the body (figure 2).

(3) ***The autonomic nerves*** **:** These include both ***sympathetic*** and ***parasympathetic nerve fibres***, and they control the ***involuntary functions*** allover the body (see below).

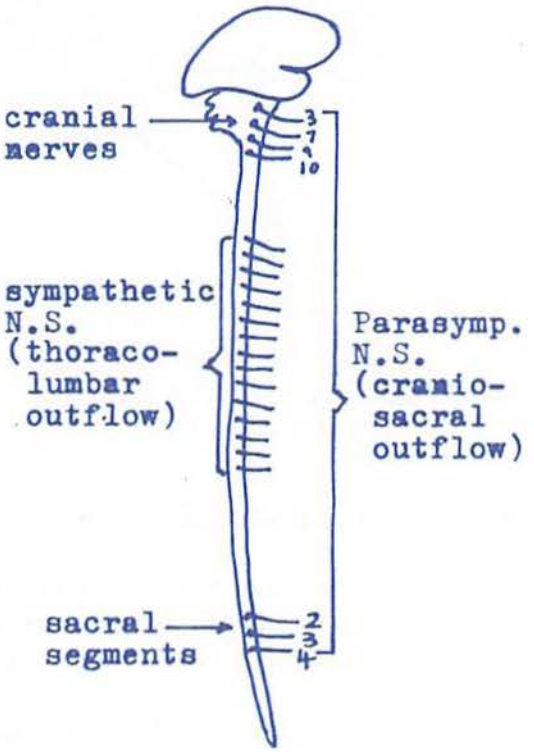


Figure 3 : Divisions of the A.N.S.

DIVISIONS OF THE A.N.S.

The A.N.S. is divided into the following 2 systems :

(1) The sympathetic nervous system : This arises from the lateral horn cells of all thoracic and upper 3 lumbar segments of the spinal cord, so it is also called the ***thoracolumbar outflow*** (figure 3).

(2) The parasympathetic nervous system : This arises from the 2nd, 3rd and 4th sacral segments of the spinal cord as well as from the nuclei of some cranial nerves, which are the following :

(a) The 3rd cranial nerve (= ***Oculomotor nerve***).
(b) The 7th cranial nerve (= ***Facial nerve***).
(c) The 9th cranial nerve (= ***Glossopharyngeal nerve***).
(d) The 10th cranial nerve (= ***Vagus nerve***).

Therefore, the parasympathetic nervous system is also called the ***craniosacral outflow*** (figure 3).

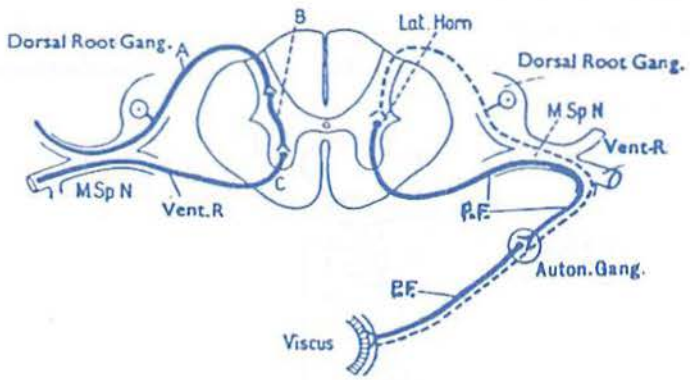


Figure 4 : The autonomic reflex arc (on the right) compared with the somatic reflex arc (on the left). P.F. before the autonomic ganglion is preganglionic fibre and P.F. after the ganglion is postganglionic fibre. M.Sp.N. = Mixed Spinal Nerve. A = afferent neuron. B = intermediate neuron. C = efferent neuron, vent. R = ventral root.

General arrangement of the A.N.S.

Impulses initiated in visceral receptors are relayed via afferent autonomic nerve fibres to the nervous system which, in turn, controls the visceral functions by discharging impulses to the viscera via efferent autonomic nerve fibres.

The efferent autonomic nerve fibres arise from the ***lateral horn cells in the grey matter of the spinal cord***, and from some ***cranial nerve nuclei*** (in case of the cranial parasymp.outflow). They proceed ***outside the nervous system to the autonomic ganglia*** (see below) where they ***relay*** (= ***synapse***) with their nerve cells. From such ganglia, other neurons arise and proceed to the effector organs (figure 4). The nerve fibres that originate from the nervous system are called ***preganglionic nerve fibres*** (or neurons), while those arising from the autonomic ganglia are called ***postganglionic nerve fibres*** (or neurons).

The presence of ***autonomic ganglia*** is a characteristic feature of the A.N.S. The ***preganglionic neurons belong to type B nerve fibres*** (refer to nerve and muscle) and are mostly ***myelinated*** (so they have a ***white colour***). On the other hand, the ***postganglionic neurons belong to type C nerve fibres*** and are mostly ***unmyelinated*** (so they have a ***grey colour***).

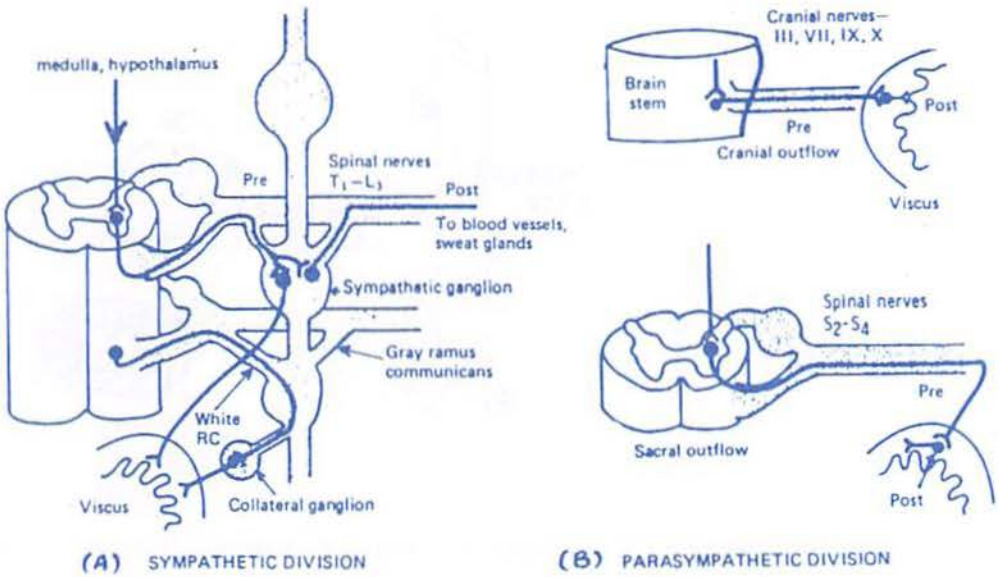


Figure 5 : Course of sympathetic (A) and parasympathetic (B) efferent nerve fibres. Pre = preganglionic neuron. Post = postganglionic neuron. RC = Ramus Communicans.

Course of the symp. and parasymp. efferent fibres

(A) The sympathetic efferent nerve fibres : The preganglionic neurons leave the ventral (= anterior) roots of the thoracic and upper lumbar spinal nerves, and enter the ***white rami communicans*** (***white RC***). Through these rami, these neurons reach the ***lateral and collateral autonomic ganglia*** (see below), in which they synapse with the cell bodies of the postganglionic neurons (figure 5 A).

Some of the postganglionic neurons pass to the viscera, while others turn back and join the spinal somatic nerves (passing through other pathways called the ***grey rami communicans***) and are distributed to the autonomic effector structures ***in the skin and skeletal muscles*** e.g. the sweat glands and blood vessels (figure 5 A).

(B) The parasympathetic efferent nerve fibres : The preganglionic neurons in both the cranial and sacral outflows end mostly at ***terminal autonomic ganglia*** from which short postganglionic neurons arise and supply the effector organs (figure 5 B).

THE AUTONOMIC GANGLIA

There are 3 types of autonomic ganglia, which are the following (figure 6):

(1) Lateral (= vertebral or paravertebral) ganglia : These are present in the form of 2 chains at both sides of the vertebral column, each containing ***about 23 ganglia*** connected together by nerve fibres. The 2 chains

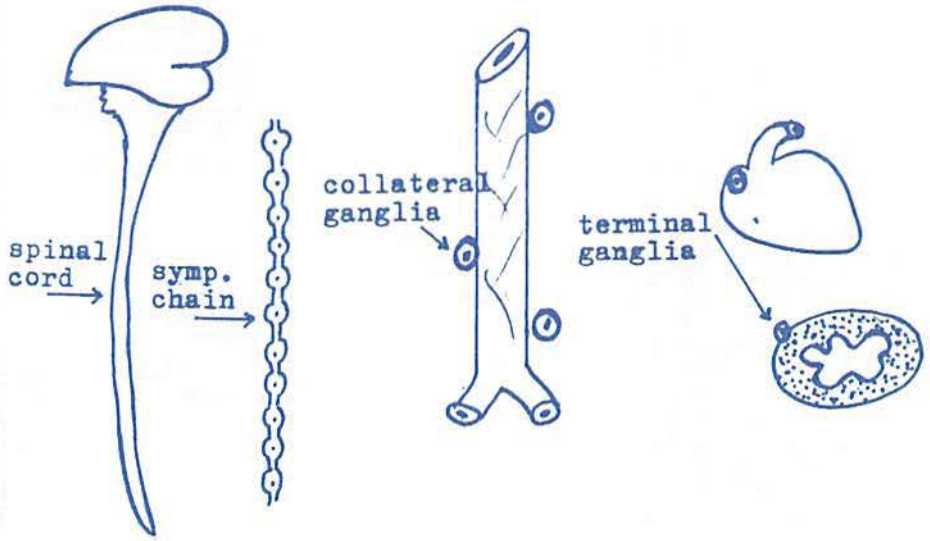


Figure 6 : The various autonomic ganglia.

are called the ***sympathetic chains*** (figure 6) because they are the main sites where the sympathetic preganglionic neurons relay (figure 5 A).

They include ***3 cervical ganglia*** (superior, middle and inferior), ***12 thoracic ganglia***, ***4 lumbar ganglia***, ***4 sacral ganglia*** and usually ***one coccygeal ganglion***. Sometimes, the inferior cervical and upper thoracic ganglia fuse together forming a ganglion called ***the stellate ganglion***.

(2) Collateral (= prevertebral) ganglia : These are present mainly in the abdomen ***in close relation to the aorta and its big branches*** (figure 6), and they carry the names of their corresponding arteries e.g. ***the celiac, superior and inferior mesenteric ganglia***. Similar to the lateral group of ganglia, these ganglia are ***mostly the site of relay of sympathetic preganganglionic neurons*** (figure 5 A).

(3) Terminal (= peripheral) ganglia : These are present near (or in the walls of) the effector organs, specially in the walls of the pelvic viscera and the heart (figure 6). Those embedded in the visceral walls are called ***intramural ganglia*** (figure 5 B). As described above, these ganglia are ***mostly the site of relay of parasympathetic preganglionic neurons***.

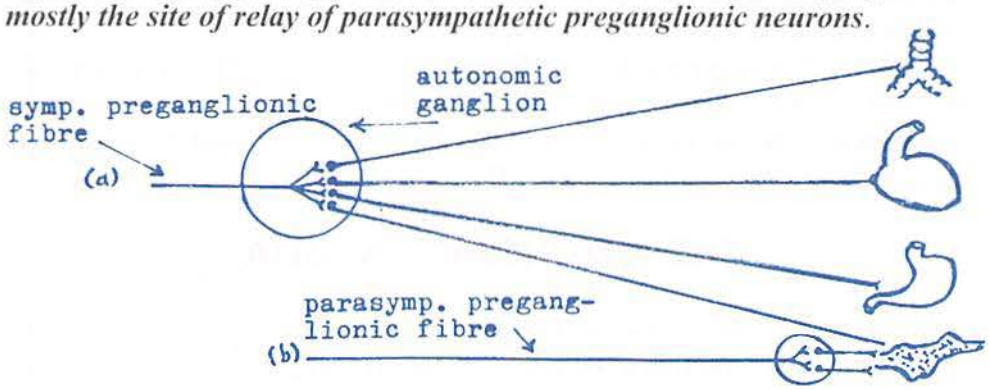


Figure 7 : Divergence of preganglionic fibres in the autonomic ganglia.

Functions of the autonomic ganglia

The autonomic ganglia provides ***a spreading mechanism for signals through divergence of the preganglionic fibres in these ganglia*** (figure 7). Such function is *apparent in case of sympathetic preganglionic fibres* because they relay at ganglia that are situated away from the effector organs (***the lateral and collateral ganglia***), which permits marked divergence and spreading of the sympatheic impulses (figure 7 a) leading to ***generalized sympathetic functions***, which is beneficial because ***the sympathetic system is always required to act as a whole*** (page 18).

On the other hand, the parasympathetic preganglionic fibres relay at ganglia that are situated close to the effector organs (the ***terminal and intramural ganglia***) which limits the divergence and spreading of parasympathetic impulses (figure 7 b) leading to ***localized parasympathetic functions*** (which is also beneficial, since ***generalized parasympathetic functions are undesirable and may be dangerous or even fatal***).

Determination of the site of relay in autonomic ganglia

(1) Langley's nicotine test : The ganglion is painted with ***a large dose of nicotine,*** then the preganglionic fibre is stimulated (figure 8 A). If no response is obtained, this indicates that the preganglionic fibre has relayed in this ganglion (because the large dose of nicotine paralyzes the ganglion cells). Conversely, if a response is obtained, this indicates that the preganglionic fibre has passed through this ganglion without relay.

(2) Histological (= degeneration) method : The preganglionic fibre is cut and its degeneration is traced. ***Stoppage of the degeneration process at the ganglion indicates that this fibre has relayed*** in this ganglion, but extension of the degeneration process beyond the ganglion indicates that this fibre has passed through this ganglion without relay (figure 8 B).

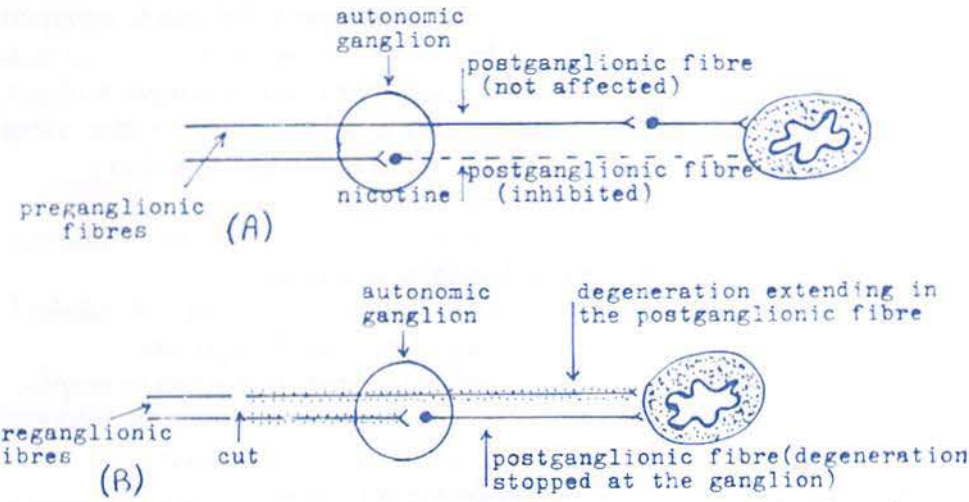


Figure 8 : Determination of the site of relay of preganglionic fibres in autonomic ganglia. **(A)** Langley's nicotine test. **(B)** Histological method.

THE SYMPATHETIC NERVOUS SYSTEM

The sympathetic N.S. can be divided into **4 divisions** which are the ***cervical***, ***cardio-pulmonary***, ***splanchnic*** and ***somatic*** divisions.

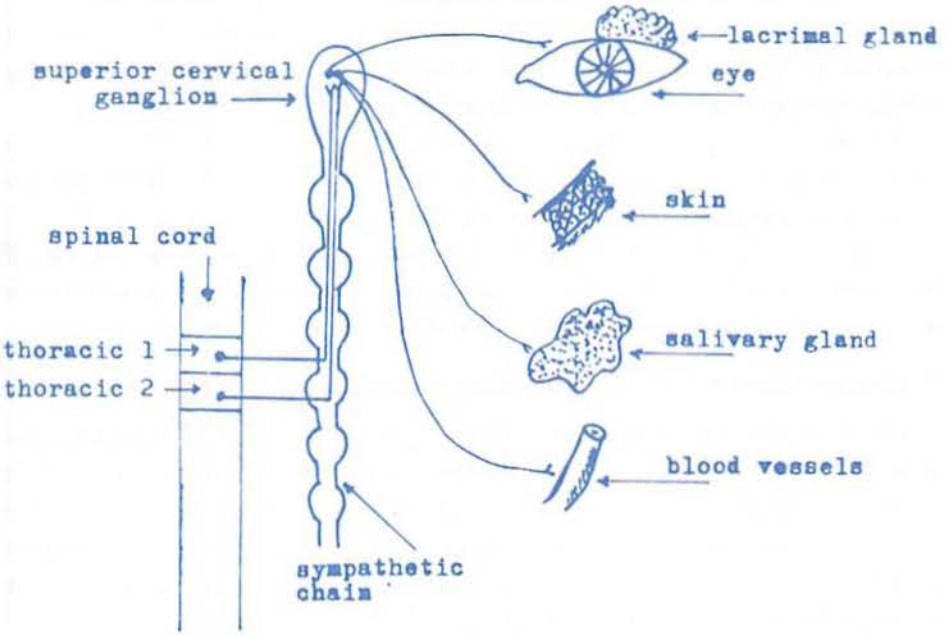


Figure 9 : The cervical sympathetic division.

(1) THE CERVICAL SYMPATHETIC DIVISION

This division supplies various structures in the region of the ***head and neck***. It arises from the lateral horn cells of the ***upper 2 thoracic segments*** of the spinal cord. Preganglionic fibres reach the sympathetic chain then they proceed upwards and relay in the ***superior cervical ganglion*** (figure 9). Postganglionic neurons arise from this ganglion then they pass along branches of the carotid arteries and supply the following structures :

(1) The eyes, in which sympathetic stimulation causes :

(a) Contraction of the radial muscle of the iris (= dilator pupillae muscle) leading to ***mydriasis*** (= ***pupil dilatation or dilation***).

(b) Contraction of muscles in the eyelids (called the superior and inferior tarsal muscles) leading to ***widening of the palpebral fissure***.

(c) Contraction of Muller's muscle behind the eyeballs leading to ***exophthalmos*** (= forward protrusion of the eyeballs), specially in animals.

(d) V.C. (= ***VasoConstriction***) of the blood vessels of the eye.

(e) Relaxation of the ciliary muscle ***during far vision***.

(2) The salivary glands,in which sympathetic stimulation causes ***V.C.*** as well as**(a)**Little viscous concentrated secretion (= ***trophic secretion***) and

(b) Squeezing of the salivary secretion as a result of contraction of the ***myoepithelial cells*** that surround the salivary acini.

(3) The lacrimal glands, in which sympathetic stimulation produces V.C. and a little ***trophic secretion***.

(4) The skin of the head and neck, in which sympathetic stimulation causes **(a)** V.C. **(b)** Sweat secretion. **(c)** Hair erection (as a result of contraction of the ***erector pilae (or pilomotor) muscles in the skin***).

(5) The cerebral vessels, in which sympathetic stimulation causes ***weak V.C.***

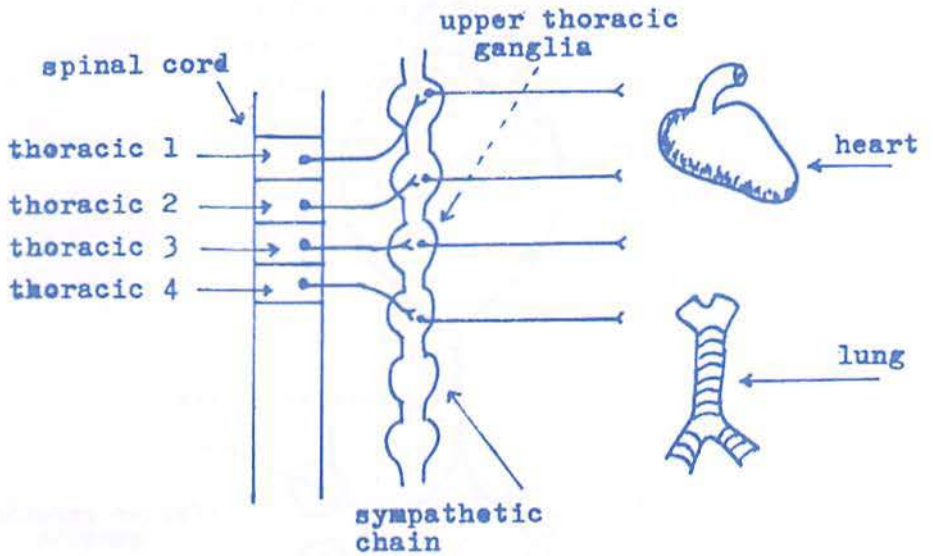


Figure 10 : The cardio-pulmonary sympathetic division.

(2) THE CARDIO-PULMONARY SYMPATHETIC DIVISION

This division supplies the ***heart and lungs***. It arises from the lateral horn cells of the ***upper 4 thoracic segments*** of the spinal cord. Preganglionic neurons reach the sympathetic chain, where they relay in the ***lower cervical and upper 4 thoracic ganglia***, from which postganglionic neurons arise and supply the following structures (figure 10) :

(1) The heart : Sympathetic stimulation activates the heart through ***increasing all properties of its muscle*** (= ***the cardiac muscle***). So the heart accelerates, its contraction becomes stronger, and its excitability and speed of conductivity (to impulses) are much increased.

(2) The coronary vessels (= vessels that supply the cardiac muscle) : Sympathetic stimulation leads to ***V.D.*** (= ***vasodilatation***) of these vessels.

(3) The bronchioles : Sympathetic stimulation ***inhibits secretion of mucus*** from the bronchial glands and produces ***bronchodilatation***.

(4) Pulmonary vessels (= *vessels in the lungs*), in which sympathetic stimulation leads to ***V.C.***.

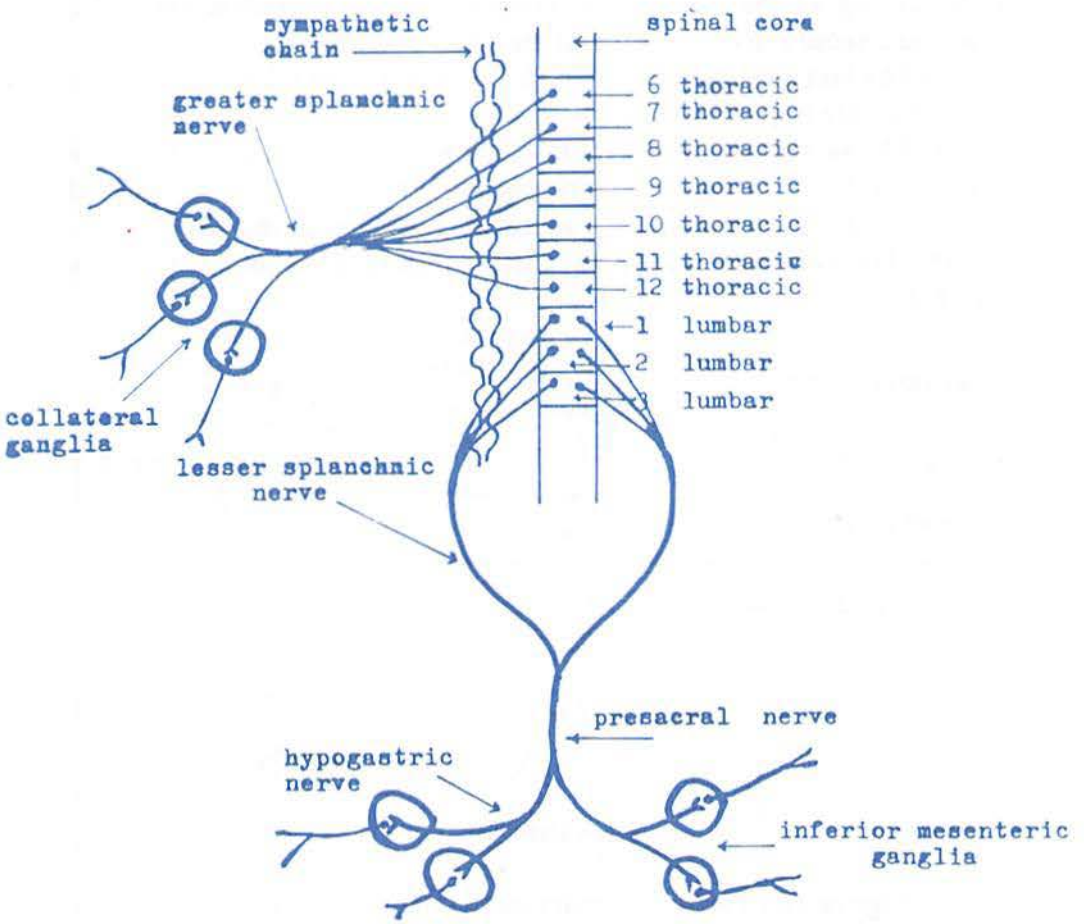


Figure 11 : The splanchnic nerves.

(3) THE SPLANCHNIC (VISCERAL) SYMPATHETIC DIVISION

This division supplies various ***abdominal and pelvic viscera***. It arises from the lateral horn cells of the ***lower 6 - 7 thoracic and upper 3 lumbar segments*** of the spinal cord. Preganglionic neurons each the sympathetic chain where ***they pass without relay*** (figure 11), then they divide into the following ***2 splanchnic nerves*** (which contain ***preganglionic neurons***) :

(A) The greater splanchnic nerve

The preganglionic fibres that constitute this nerve originate from the lateral horn cells of the 5^{th}-12^{th} ***thoracic segments*** of the spinal cord and relay mostly in the ***collateral ganglia in the abdomen*** (page 6), except those supplying the ***adrenal medulla, which relay inside this gland*** (see below). From these ganglia, postganglionic neurons arise and supply the ***abdominal viscera*** producing the following effects (or functions) :

(1) V.C. of the majority of the arterioles in the stomach, small intestine, proximal part of the large intestine, kidneys, pancreas and liver, and ***V.D. of some of these arterioles*** (see below).

(2) Relaxation of the walls of the stomach, small intestine and proximal part of the large intestine and contraction of their corresponding sphincters (leading to ***food retention***). Gastrointestinal secretions are also reduced.

(3) Contraction of the smooth muscle in the ***capsule of the spleen,*** so pouring its stored concentrated blood (about 50 ml) into the bloodstream.

(4) Stimulation of ***glycogenolysis in the liver*** (= breakdown of glycogen into glucose molecules) thus ***increasing the blood glucose level***.

Sympathetic stimulation also ***increases the metabolic rate*** (a thermogenic effect) and stimulates ***lipolysis*** in adipose tissue (thus increasing both the blood glucose and free fatty acid levels).

(5) Stimulation of the adrenal medulla to secrete hormones known as ***catecholamines***, which include mainly ***adrenaline*** (= ***epinephrine***) and ***noradrenaline*** (= ***norepinephrine***). The preganglionic fibres that supply this gland pass through various autonomic ganglia ***without relay*** till reaching the gland in which they ***relay directly with its secretory cells***.

** The adrenal medulla is a **modified sympathetic ganglion** in which the ***ganglionic cells have been modified into secretory cells***, and the preganglionic fibres become the nerves that stimulate their secretion.

** Stimulation of the sympathetic nervous system increases the arterial blood pressure ***in 2 stages***, the first is due to the increase in activity of the heart and the generalized V.C., while the second is due to secretion of catecholamines from the adrenal medulla (which increase these effects).

(B) The lesser splanchnic nerve

The preganglionic fibres that constitute this nerve originate from the lateral horn cells of the ***upper 3 lumbar segments*** of the spinal cord. The 2 nerves from both sides unite together forming the ***presacral nerve*** which proceeds to the pelvis, where it divides into ***2 hypogastric nerves*** (figure 11) These nerves relay in ***terminal ganglia*** called *inferior mesenteric* (*or hypogastric*) *ganglia* from which postganglionic neurons arise and supply the ***pelvic viscera***, producing the following effects (or functions) :

(1) Relaxation of the muscle in the urinary bladder wall (detrusor muscle) and contraction of the internal urethral sphincter leading to ***urine retention***

(2) Relaxation of the walls of the rectum and distal part of large intestine and contraction of the internal anal sphincter leading to ***retention of feces***.

(3) V.C.. of blood vessels in the pelvic viscera as well as in the. erectile tissues (= penis in males and clitoris in females) leading to ***inhibition of erection and shrinkage of these organs***.

(4) In males, it causes contraction of the smooth muscle in the vas deferens, seminal vesicles & ejaculatory ducts leading to ***ejaculation of semen***.

(5) In females, it produces ***variable effects on the uterus*** i.e. contraction or relaxation (depending on the stage of menstrual cycle, the ovarian hormonal blood level, pregnancy and other factors).

(4) THE SOMATIC DIVISION OF THE SYMPATHETIC N.S.

This division of the sympathetic nervous system ***accompanies the somatic nerves*** (which arise from the ***anterior horn cells***) and supplies **the skin and skeletal muscles**. The sympathetic postganglionic neurons that constitute this division ***arise from the sympathetic chain***, turn back in the ***grey rami communicans*** and join the spinal somatic nerves (figure 5 A). Those which supply the upper limbs arise from 4^{th} - 8^{th} thoracic segments and reach them via the ***brachial plexuses***, while those which supply the lower limbs arise from 10^{th} - 12^{th} thoracic segments and reach them via the ***lumbosacral plexuses***.

Functions of the sympathetic nerves in the skin

(1) V.C. **(2)** Sweat secretion. **(3)** Hair erection (= horripilation).

Functions of the sympathetic nerves in the skeletal muscles

. The skeletal muscles receive both ***noradrenergic sympathetic nerve fibres*** (mainly cause V.C.) as well as ***cholinergic sympathetic nerve fibres*** (cause strong V.D.). Accordingly, sympathetic stimulation may cause V.C. or V.D. in the skeletal muscles, depending on the underlying condition e.g. in case of hemorrhage, V.C. predominates (which helps elevation of the arterial blood pressure) while during muscular exercise, V.D. predominates (which increases the blood supply to active muscles). Sympathetic stimulation also ***accelerates the chemical reactions*** in the active muscles, and this together with V.D. lead to a stronger contraction, delayed fatigue and early recovery after exercise.Such effect was called the **Orbelli effect**.

HORNER'S SYNDROME

An injury to the ***cervical sympathetic nerve fibres*** produces a syndrome (= group of symptoms) ***on the same (i.e. affected) side*** called **Horner's syndrome,** the symptoms of which include the following **:**

(1) Ptosis i.e. drooping of the upper eyelid (which will cover the eye) due to paralysis of the superior tarsal muscle.

(2) Miosis (= *pupilloconstriction*) due to paralysis of the dilator pupillae muscle.

(3) Anhydrosis (= *absence of sweat secretion*).

(4) V.D. (due to loss of the sympathetic V.C effect), so the affected side becomes ***warmer and more red*** than the healthy side.

(5) Enophthalmos (= sinking of the eyeball backward in the orbit) due to paralysis of Muller's muscle (not prominent in man).

CHEMICAL TRANSMISSION IN THE SYMPATHETIC N.S.

The nerves control the activity of their effector organs through liberating (or releasing) chemical substances from their endings known as the ***chemical transmitters***. In case of the sympathetic nervous system, the ***pregnaglionic fibres liberate acetylcholine***, so these fibres are called ***cholinergic fibres***. On the other hand, ***most sympathetic postganglionic neurons liberate noradrenaline*** (so these fibres are called ***noradrenergic fibres***), ***but some of these neurons are cholinergic*** (see below).

Steps of synthesis of noradrenaline

(1) The amino acid ***phenylalanine*** is hydroxylated into the amino acid ***tyrosine*** by activity of the enzyme *phenylalanine hydroxylase*.

(2) Tyrosine is then hydroxylated to ***DOPA*** (=dihydroxyphenylalanine) by activity of the enzyme *tyrosine hydroxylase*.

(3) DOPA is converted to ***dopamine*** *by* activity of the enzyme *DOPA-decarboxylase*.

(4) Dopamine is oxidized to ***noradrenaline*** by activity of the enzyme *dopamine beta hydroxylase*.

** Adrenaline can then be formed in the adrenal medulla (and also by certain neurons in C.N.S.) by ***methylation of noradrenaline*** under effect of the ***PNMT*** enzyme (= Phenylethanolamine-N-Methyl-Transferase).

Both ***adrenaline and noradrenaline as well as dopamine are known as the catecholamines***

Inactivation (or fate) of catecholamines

This occurs by the following mechanisms **:**

(1) ***Active re-uptake*** into the vesicles at the nerve endings which have released them.

(2) ***Oxidation*** of both adrenaline and noradrenaline by activity of the enzyme mono-amine oxidase (**MAO**) to ***dihydroxy-mandelic acid***.

(3) ***Methylation*** of both adrenaline (= epinephrine) and noradrenaline (= norepinephrine) into ***metanephrine and nor-metanephrine*** respectively by activity of the ***Catechol-O-Methyl-Transferase*** enzyme (***COMT***).

Sites of release of catecholamines

(1) *Most sympathetic postganglionic nerve endings release noradrenaline*

(2) ***The adrenal medulla*** : This gland secretes mainly in ***emergency conditions*** to support the actions of the sympathetic nervous system e.g. muscular exercise, hemorrhage (and other conditions of hypotension), hypoglycemia, hypothermia and emotions. Its secretion is usually ***80 % adrenaline and 20 % noradrenaline***.

(3) ***Certain neurons in the C.N.S.*** release noradrenaline, others release adrenaline, and still other neurons release dopamine.

The sympathetic cholinergic fibres

The sympathetic *postganglionic* neurons liberate ***acetylcholine*** (and not noradrenaline) **at 2 sites**. Accordingly, these neurons are called ***sympathetic cholinergic fibres***, and they include the following :

(1) The sympathetic postganglionic neurons that supply ***the eccrine sweat glands*** (those responsible for body temperature regulation).

(2) Some sympathetic postganglionic neurons that supply ***the skeletal muscles***. These neurons cause V.D. (page 12) and are part of a system called the **sympathetic V.D. system**. This system originates in the cerebral cortex by neurons that descend and relay in the hypothalmus, from which other neurons arise and pass through the medulla oblongata without relay till the lateral horn cells of the spinal cord. From these cells, sympathetic preganglionic neurons arise and proceed to relay in the sympathetic chain ganglia, from which postganglionic neurons arise and proceed to the skeletal muscles along the somatic division of the sympathetic nervous system (page 12). Such V.D. system discharges mainly during **(a)** ***Emotions*** (and is probably the cause of hypotension and fainting that may occur in these conditions) **(b)** ***Muscular exercise*** (and is partly responsible for the increased blood flow in the active skeletal muscles).

The sympathetic V.D. fibres

The sympathetic nerve fibres generally produce V.C. However, in certain sites they produce V.D. , so these nerve fibres are called the sympathetic V.D. fibres. They include the following :

(1) The sympathetic nerves that supply the heart : In fact, noradrenaline released by these nerves ***produces V.C. in the coronary vessels***. However, because sympathetic stimulation also increases the cardiac activity, ***several V.D. metabolites accumulate*** in the cardiac muscle, and the V.D. effect of these metabolites overcomes the V.C. effect of noradrenaline , so the net result is coronary V.D.

(2) The sympathetic cholinergic nerves that supply the skeletal muscles : These lead to V.D. when stimulated e.g. in conditions of emotions and muscular exercise (see the sympathetic V.D. system above).

(3) Some sympathetic nerves that supply the splanchnic area : These fibres are *probably cholinergic*.The V.D.effect may also be due to predomination of *$beta_2$ adrenergic receptors* in some splanchnic vessels (see next)

THE ADRENERGIC RECEPTORS

The various effects of catecholamines are produced through acting on 2 types of receptors in the tissues called the **alpha and beta receptors**.

(1) The alpha receptors

There are 2 main subtypes of these receptors called ***alpha $_1$ and alpha $_2$ receptors***. Both ***generally produce excitatory effects*** e.g. V.C. of blood vessels (arterioles and systemic veins) and contraction of muscles (e.g. the dilator pupillae muscle, erector pilae muscles, various sphincters, spleen capsule muscles and those which cause ejaculation of semen). However, ***in certain sites they produce inhibitory effects*** (particularly the ***alpha $_2$ receptors***) e.g. *in the stomach and intestinal walls and the islets of Langerhans of the pancreas* (table 1).

(2) The beta receptors

There are 2 main subtypes of these receptors called **beta $_1$ and beta $_2$ receptors**. However, there are also **beta $_3$ receptors** in some areas (specially in the ***adipose tissue***).

(a) Beta $_1$ receptors : These produce mainly ***excitatory effects*** and are located ***mainly in the heart*** (in addition to some other tissues e.g. the adipose tissue and the juxtaglomerular cells in the kidneys). However, in certain areas ***they produce inhibitory effects e.g. in the intestinal wall*** (table 1).

(b) Beta $_2$ receptors : These generally produce ***inhibitory effects*** e.g. V.D. of vessels (arterioles and systemic veins) and relaxation of the bronchial muscle, ciliary muscle, the spleen capsule muscles and the walls of the stomach, intestine and urinary bladder. However, in certain sites ***they produce excitatory effects e.g. in the liver, heart and islets of Langerhans of the pancreas*** (table 1).

Many organs contain ***both types of adrenergic receptors*** (table 1). In this case, one of the following effects may occur :

(1) Both may produce ***excitatory effects*** e.g. in the liver and salivary glands.

(2) Both may produce ***inhibitory effects*** e.g. in the stomach and intestinal walls.

(3) Both may produce ***antagonistic effects*** e.g. in the coronary, pulmonary, abdominal and skeletal muscle blood vessels, the spleen capsule and islets of Langerhans of the pancreas. In this case, the final effect depends on ***which of them is predominant*** e.g. in the spleen and most blood vessels, the alpha receptors predominate, thus the net result of sympathetic stimulation at these sites will be contraction of the splenic capsule and V.C. .

Table (1) : Types of adrenergic receptors in various organs and effects of stimulation.

Organ	Type of receptor	Effect of stimulation
S-A node of the heart	Beta 1 and 2	Increase in the heart rate
Atria, ventricles, A-V node and the conduction system of the heart	Beta 1and 2	Increase contractility, rhythmicity, conductivity and excitability
Coronary vessels	Alpha 1 & 2 and beta 2	Alpha cause V.C. and beta cause V.D.
Dilator pupillae muscle	Alpha 1	Contraction (pupil dilation)
Ciliary muscle	Beta 2	Relaxation for far vision
Bronchial muscle	Beta 2	relaxation
Pulm.and abdominal vessels and arterioles in skeletal muscles	Alpha 1 and beta 2	Alpha cause V.C. and beta cause V.D.
Cerebral vessels	Alpha 1	V.C.
Skin vessels	Alpha 1 and 2	V.C.
Erector pilae muscle	Alpha 1	contraction
Sweat glands	Alpha 1	Slight localized secretion
Salivary glands	Beta and alpha 1 & 2	Alpha cause thick viscous secretion & V.C., and beta cause amylase secretion
Sphincters of GIT	Alpha 1	contraction
Stomach wall	Alpha 1 & 2 and beta 2	All cause relaxation
Gastric secretion	Alpha 2	inhibition
Intestinal motility and tone	Alpha 1 & 2 and beta 1 & 2	All decrease motility and tone
Spleen capsule	Alpha 1 and beta 2	Alpha cause contraction and beta cause relaxation
Liver	Alpha 1 and beta 2	Both cause glycogenolysis
Adipose tissue	Alpha 1 and beta 1 & 3	Increase lipolysis
Juxtaglomerular cells	Beta 1	Increase renin secretion
urinary bJadder & gallbladder	Beta 2	Relaxation
Internal urethral sphincter	Alpha 1	Contraction
Uterus	Alpha 1 and beta 2	Alpha cause contraction and beta cause relaxation
Islets of Langerhans in the pancreas	Alpha 2 and beta 2	Alpha decrease secretion and beta increase secretion
Pancreatic acini	Alpha	Decrease secretion
Male sex organs	Alpha 1	Ejaculation

Differences between adrenaline and noradrenaline

Both catecholamines act on the 2 types of adrenergic receptors, and produce their effects by increasing the intracellular content of ***cyclic AMP***. However, ***noradrenaline has a greater affinity for alpha receptors*** while

adrenaline has a greater affinity for beta receptors (specially the beta 2 receptors). Accordingly, adrenaline is characterized by the following :

(1) It exerts ***a weaker V.C. effect*** than noradrenaline (the latter causes potent V.C. allover the body ***except in the coronary vessels***, so it is more useful in the treatment of shock).

(2) It exerts ***more metabolic effects*** than noradrenaline (adrenaline markedly increases the metabolic rate and the blood glucose and free fatty acid levels, as well as the blood fibrinogen level).

(3) It produces ***more relaxation of the bronchial muscle*** than noradrenaline does (so it is more useful in the treatment of bronchial asthma).

(4) It produces ***more excitation of the heart and more coronary V.D.***

Sympathomimetic drugs (Adrenergic agonists or stimulants)

These are drugs that exert actions ***similar to those produced by sympathetic stimulation***. The most important of these drugs are the following :

(1) Drugs that release noradrenaline from the sympathetic postganglionic nerve endings e.g. ***tyramine, ephedrine and amphetamine***.

(2) Drugs that stimulate the alpha receptors e.g. ***phenylephrine***.

(3) Drugs that stimulate the beta receptors e.g. ***isoproterenol & salbutamol***

Sympatholytic drugs (Adrenergic antagonists or biockers)

These are drugs that ***block (or depress) the actions of the sympathetic nervous system*** The most important of these drugs are the following :

(1) Drugs that block conduction in the sympathetic ganglia e.g ***arfonad*** and ***hexamethonium***.

(2) Drugs that block synthesis of norepinephrine e.g. ***metyrosine***.

(3) Drugs that prevent storage of norepinephrine e.g. ***reserpine***.

(4) Drugs that prevent release of norepinephrine e.g. ***guanethidine***.

(5) Drugs that lead to formation of false transmitters e.g. ***methyldopa***.

(6) ***Alpha receptor blockers*** e.g. ***ergotoxin***, ***prazosin*** (blocks alpha $_1$ receptors only) and ***yohimbine*** (blocks alpha $_2$ receptors only).

(7) ***Beta receptor blockers*** e.g. ***propranolol*** and ***atenolol***.

** Sympathetic stimulation (or catecholamine injection) can lower the arterial blood pressure *after giving an alpha receptor blocker*. In this case, the beta receptors remain active and produce V..D., so the peripheral resistance is decreased and consequently, the arterial blood pressure falls .

General functions of the sympathetic N.S.

(1) The Sympathetic tone

This is *continuous discharge of impulses in the sympathetic nerves* that supply the arterioles and venules ***during rest***. It leads to ***partial V.C.***

which is important because it produces ***peripheral resistance*** to blood flow, and this is essential for ***maintenance of the arterial blood pressure particularly the diastolic pressure*** (refer to circulation).

(2) Role of the sympathetic N.S. in emergency conditions

In emergency conditions (e.g. muscular exercise, hemorrhage, hypoglycemia, hypothermia and severe emotions), the sympathetic N.S. is stimulated and its effects are increased by ***catecholamines*** secreted from the adrenal medullae. This is essential for ***adaptation and survival in such conditions***, which occurs through the following mechanisms :

(A) Resisting threatening dangers e.g. in cases of hemorrhage, the danger of hypotension and shock is antagonized by ***generalized V.C.*** (which increases the peripheral resistance), ***heart acceleration*** (which increases the cardiac output) and contraction of the ***spleen capsule*** (which shifts its stored blood into the general circulation). In addition, ***bronchodilatation*** occurs (which helps better ventilation) and the ***blood fibrinogen level is increased*** (which accelerates blood clotting and helps hemostasis).

(B) Producing better muscular performance when required (e.g. for preparation for ***fight or flight***) through producing the following effects :

(1) ***Heart acceleration*** : This increases both the cardiac output and blood pressure (providing better blood perfusion to the active muscles).
(2) ***V.C. in the splanchnic area and skin*** : This increases the blood pressure and shifts blood to the coronary and skeletal muscle blood vessels (in which V.D. occurs). In the muscles, V.D. occurs by effect of the sympathetic V.D. system (page 14), and it leads to better contraction and delayed onset of fatigue (= Orbelli effect, page12).
(3) ***Increase of blood glucose & free fatty acid levels*** (supply energy).
(4) ***Contraction of the spleen capsule*** (shifts blood to the circulation).
(5) ***Bronchodilatation*** (which helps better ventilation).
(6) ***Increase of alertness (= arousal state)*** by a central action of catecholamines on the reticular formation.
(7) ***Increase of sweat secretion*** (which helps loss of the excessive heat produced during exercise as a result of the increased metabolism).
(8) ***Pupillodilatation and widening of the palpebral fissure*** (which increase the visual efficiency).

** The sympathetic nervous system is **catabolic** because it mobilizes energy from its stores to be used by the body (so it is also called the ***catabolic nervous system***). It acts ***as a whole*** both at rest (to produce the sympathetic tone) as well as during emergency conditions (see above). This is produced as a result of relay of the sympathetic preganglionic neurons in lateral and collateral autonomic ganglia, which allows ***divergence*** of the sympathetic signals to activate many organs at the same time (figure 7 a).

THE PARASYMPATHETIC NERVOUS SYSTEM

The parasympathetic nervous system is a 2-neurons system (consisting of preganglionic and postganglionic neurons) and ***most parasympathetic preganglionic neurons relay in terminal ganglia*** that lie either close to the effector organ or in its wall (= ***intramural ganglia***), which results in ***minimal divergence*** (figure 7 b) and ***more localized actions***. In intramural ganglia, the postganglionic neurons are very short and lie entirely in the walls of the supplied organs (figures 5 B and 16). The parasympathetic nervous system consists of the ***cranial and sacral outflows*** (figure 3).

The cranial parasympathetic outflow

This is present in the ***3rd, 7th, 9th and 10th cranial nerves*** (page 4).

(A) The oculomotor (3rd cranial) nerve

The preganglionic fibres arise from part of the oculomotor nerve nucleus in the *midbrain* called the ***Edinger-Westphal nucleus***. They run in the oculomotor nerve and relay in the ***ciliary ganglion*** (behind the eyeball) from which postganglionic fibres arise and form the ***short ciliary nerves***. These nerves supply the following structures in the eye (figure 12) :

(1) The pupilloconstrictor muscle, the contraction of which causes ***miosis*** (= ***pupittoconstricHon***).

(2) The ciliary muscle, the contraction of which increases the power of the lens of the eye. This is important for ***accommodation of the eye to near vision*** (refer to special senses).

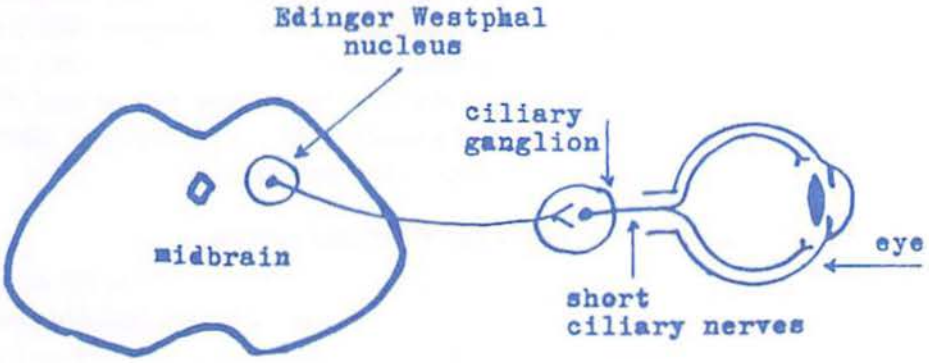


Figure 12 : The oculomotor (3rd cranial) nerve.

** It was found that the ***ciliary muscle also receives sympathetic nerves, which cause its relaxation during far vision*** (through acting on ***beta $_2$ adrenergic receptors*** in that muscle, see table I, page 16).

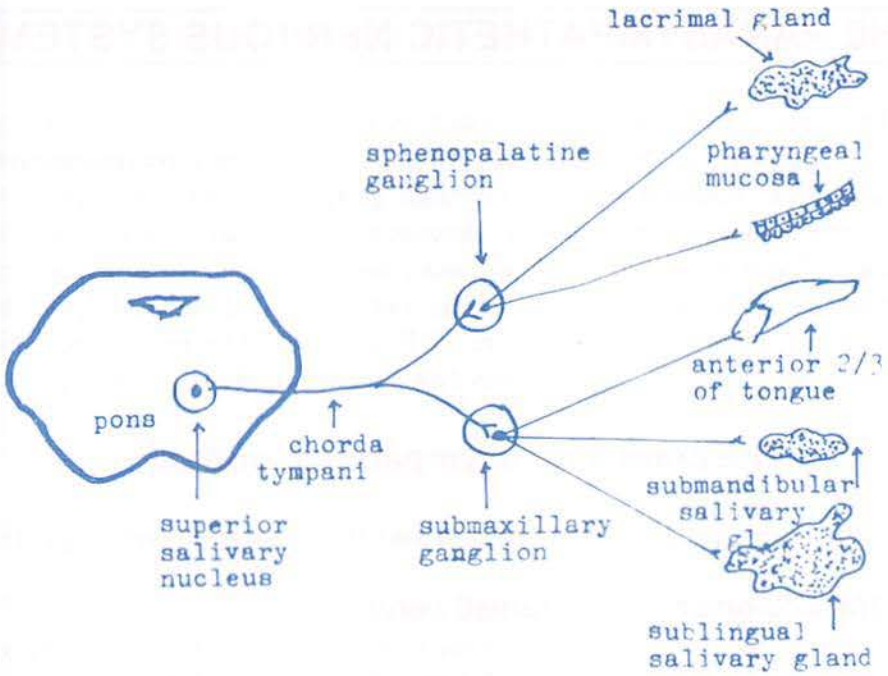


Figure 13 : The facial (7th cranial) nerve.

(B) The facial (7th cranial) nerve

The preganglionic fibres arise from part of the facial nerve nucleus in the lower part of the pons called the ***superior salivary nucleus***. They run in a nerve called **the *chorda tympani*** (branch of the facial nerve) and relay in the ***submaxillary ganglion***. Some fibres, however, relay in the ***sphenopalatine ganglion*** (figare 13).....

The postganglionic fibres that arise from the submaxillary ganglion supply the ***submandibular*** (= ***submaxillary***) ***and sublingual salivary glands and anterior 2/3 of the tongue***, while those arising from the sphenopalatine ganglion supply the ***mucosa of the soft palate and the nasopharynx as well as the lacrimal glands***. These postganglionic fibres produce both ***V.D. and secretion at their effector organs***.

(C) The glossopharyngeal (9th cranial) nerve

The preganglionic fibres arise from part of the glossopharyngeal nerve nucleus in the upper part of the medulla oblongata called the ***inferior salivary nucleus*** and relay in the ***otic ganglion***. The postganglionic fibres that arise from this ganglion supply the ***parotid salivary gland and posterior 1/3 of the tongue*** (figure 14) where they produce both V.D. and secretion.

** Parasympathetic stimulation of the salivary glands produces **true secretion** i.e a large amount of diluted saliva (compare with the ***trophic secretion*** produced by sympathetic stimulation, page 8).

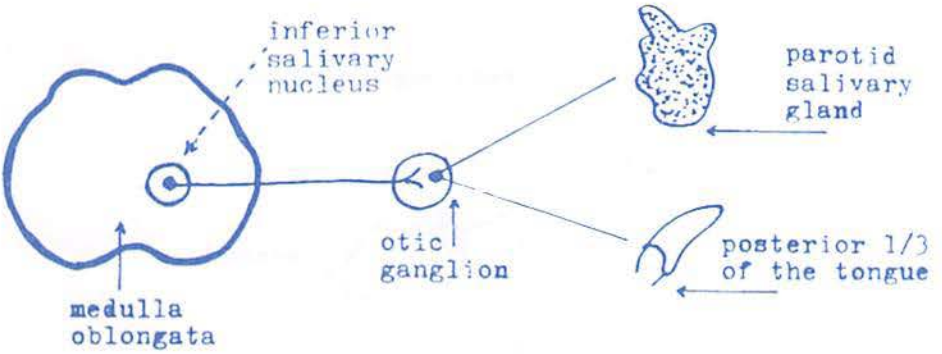


Figure 14 : The glossopharyngeal (9th cranial) nerve.

(D) The vagus (10th cranial) nerve

This constitutes 75 % of the parasympathetic fibres in the body. Its preganglionic fibres arise from the ***dorsal vagus nucleus in the medulla oblongata***, relay in ***terminal ganglia*** (as well as in the walls of the effector organs) from which short postganglionic fibres arise and supply the following organs in the chest and abdomen (figure 15) :

(1) The heart : Vagus stimulation of the heart ***inhibits all properties of the cardiac muscle*** (leading to slowing of the heart rate and a decrease in its contractility, excitability and conductivity). It also causes ***V.C. of the coronary vessels*** and reduction of the O_2 consumption of the cardiac muscle. The vagi ***do not supply the ventricles,*** and this phenomenon (or property) is called ***vagus escape*** (refer to circulation).

** Parasympathetic stimulation produces V.D. allover the body except in the coronary vessels (where it causes V.C.): The latter effect is due to ***rise in O_2 tension in the cardiac muscle*** which occurs as a result of the decrease in its metabolic activity (see above).

(2) The lungs : Vagus stimulation causes ***bronchoconstriction, mucus secretion*** from the bronchial glands and ***V.D.*** of pulmonary vessels.

(3) The gastrointestinal tract (GIT) : Vagus stimulation causes ***contraction of the walls*** of the esophagus, stomach, small intestine and proximal part of the large intestine, and ***relaxation of their corresponding sphincters***. Therefore, parasympathetic stimulation ***promotes deglutition*** (= ***swallowing***) as well as evacuation of food from the GIT.

(4) The gallbladder : Vagus stimulation helps gallbladder evacuation by causing contraction of its wall and relaxation of the sphincter of Oddi.

(5) Vagus stimulation causes **secretion** from the ***stomach*** (the gastric juice), the p***ancreas*** (the pancreatic juice and the hormones insulin and glucagon), the ***duodenum*** (mucus from Brunner's glands) and the ***liver*** (bile). In the liver. it also produces V.D. (thus increasing the hepatic blood flow).

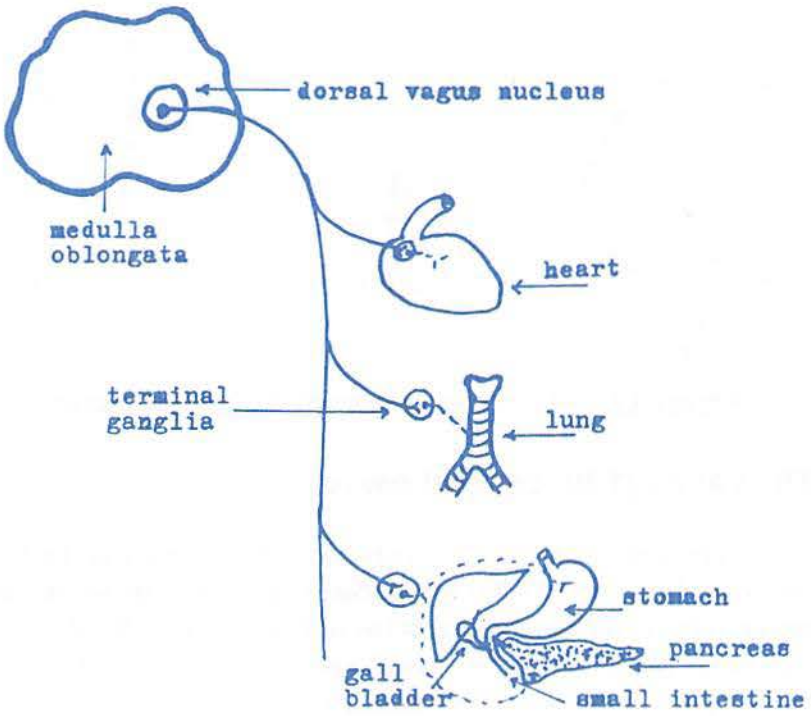


Figure 15 : The vagus (10th cranial) nerve.

The sacral parasympathetic outflow (sacral autonomic nerves)

This part of the parasympathetic N.S. originates from the ***2nd, 3rd and 4th sacral segments***, from which preganglionic fibres arise and pass through the sympathetic chain ***without relay***, then unite together forming the ***pelvic nerve or nervus erigentes*** (because it causes erection). This nerve relays in ***terminal (hypogastric) ganglia*** (and also in the walls of the pelvic viscera) from which postganglionic fibres arise and supply the following organs :

(1) The urinary bladder : Parasympathetic stimulation leads to contraction of the muscle in the wall of the urinary bladder (= ***detrusor muscle***) and relaxation of the internal urethral sphincter (resulting in ***micturition***).

(2) The rectum and distal part of the descending colon : Parasympathetic stimulation leads to contraction of the walls of these organs and relaxation of the internal anal sphincter (resulting in ***defecation***).

(3) The seminal vesicles and prostate : Parasympathetic stimulation leads to secretion from these glands.

(4) The erectile tissues (the penis in males and the clitoris in females) **:** Parasympathetic stimulation produces V.D. in these tissues (in addition to other pelvic viscera) leading to their ***erection***.

** *The **sympathetic nervous system has a much wider distribution*** than the parasympathetic nervous system.

** The parasympathetic nervous system is **anabolic** in function in contrast to the catabolic function of the sympathetic nervous system (page 18), thus it is sometimes called the ***anabolic nervous system***.

** In most organs that receive double autonomic nerve supply (from both the sympathetic and parasympathetic N.S.), they ***act in a reciprocal manner*** i.e. if one system stimulates a particular function, the other often inhibits it (e.g. in the heart, pupil, GIT, bronchioles and urinary bladder).

** Some organs receive nerve supply from ***only one of the 2 systems :***

(1) Structures supplied by sympathetic fibres only : These are the dilator pupillae muscle, skeletal muscles, skin, adrenal medulla, ventricles of the heart, and the spleen.

(2) Structures supplied by parasympathetic fibres only : These are the constrictor pupillae muscle and the esophagus.

CHEMICAL TRANSMISSION IN THE PARASYMPATHETIC N.S.

Acetylcholine synthesis and breakdown

Both ***parasympathetic preganglionic and postganglionic nerve endings*** release acetylcholine (ac.ch.) so they are ***cholinergic nerves*** (figure 16). Ac.ch. is synthesized in special vesicles in the cholinergic nerve endings by combination of ***choline*** (a nitrogenous base) with ***active acetate***. Choline is actively taken into the cholinergic neurons (and is also synthesized in these neurons) while the acetate is activated by combination of the acetate groups with reduced coenzyme A, forming ***acetyl-coenzyme A*** (= ***acetyl-CoA***). The reaction between acetyl-CoA and choline is catalyzed by the enzyme ***choline acetylase or acetyltransferase*** as follows

Acetyl-CoA + Choline $\xrightarrow{\text{choline acetylase}}$ **Ac.ch. + CoA**

Acetylcholine is then released from the vesicles by ***exocytosis*** when a signal reaches the nerve terminals (as a result of entrance of Ca^{2+} via specific voltage-gated Ca^{2+} channels).

Normally, there is ***no*** (***or very little***) ***ac. ch. in the blood*** because it is rapidly broken down after its release into its original constituents by activity of the ***cholinesterase enzyme*** (so as not to accumulate in the bloodstream, otherwise it would produce generalized actions, which are dangerous). The cholinesterase enzyme is present in high concentrations at the cholinergic nerve endings (figure 16) , and it acts as follows :

Ac.ch. $\xrightarrow{\text{cholinesterase}}$ **Acetyl-CoA + Choline**

Choline is then reuptaken back into the nerve ending, where it is used again in the synthesis of ac. ch. as described above.

Sites of release (formation) of ac.ch.

(1) ***All parasympathetic postganglionic nerve endings.***
(2) The sympathetic postganglionic nerve endings that supply the ***eccrine sweat glands and skeletal muscles*** (page 14).
(3) ***All autonomic ganglia***, at the endings of ***all preganglionic neurons*** including those supplying the ***adrenal medulla***.
(4) The neuromuscular junctions (= ***motor end plates***) i.e. at the endings of the somatic motor nerves that supply skeletal muscles.

** Ac.ch.. is also released in some synapses in the ***C.N.S.*** as well as in the ***retina of the eye***.

Muscarine and Nicotine-like actions of ac. ch.

The ***muscarine-like*** (***or muscarinic***) ***actions of ac.ch.*** are the actions of ac.ch. in **sites 1 and 2** (see above) because the *alkaloid muscarine* produces similar effects to those produced by ac.ch. in these 2 sites *if injected in the body*.

On the other hand, the ***nicotine-like*** (***or nicotinic***) ***actions of ac.ch.*** are the actions of ac.ch. in **sites 3 and 4** because *small doses of nicotine* produce similar effects to those produced by ac.ch. in these 2 sites *if injected in the body*.

Cholinergic neurons and cholinergic receptors

The cholinergic neurons are those which release ac.ch. at their endings (see above) while the cholinergic receptors are those which respond to ac.ch. The cholinergic neurons are classified into 2 types :

(1) Central cholinergic neurons : These arise from the *C.N.S.* and include ***all preganglionic neurons and the somatic nerves*** (3 and 4 above). The corresponding receptors in the autonomic ganglia and motor end plates are called ***nicotinic receptors***, because they are stimulated by small doses of nicotine (see above).

(2) Peripheral cholinergic neurons : These arise from the ***autonomic ganglia***, and include ***all parasympathetic and the sympathetic cholinergic postganglionic neurons*** (1 and 2 above). The corresponding receptors in the effector organs are called ***muscarinic receptors***, because they are stimulated by muscarine (see above) and there are ***5 different types*** of these receptors which are termed M_1 up to M_5 receptors.

** Generalized parasympathetic stimulation (or injection of ac. ch.) produces widespread V.D. allover the body which decreases the peripheral resistance leading to ***lowering of the arterial blood pressure***.

** Relay of the parasympathetic preganglionic neurons in terminal and intramural ganglia (i.e. ***close to the effector organs***) has 2 benefits :

(a) ***Production of localized actions*** **(b)** ***Potentiation of these actions***, because the transmitter at both the ganglia and the postganglionic parasympathetic nerve endings is the same i.e. ac.ch. (figure 16).

Similarly, the relay of the sympathetic preganglionic neurons in the lateral and collateral ganglia (i.e. ***away from the effector organs***) has 2 benefits **(a)** ***Production of generalized actions*** **(b)** ***Prevention of antagonistic actions at the tissues***, because the actions of ac.ch. liberated in the ganglia are often antagonistic to those produced by noradrenaline that is liberated by the sympathetic postganglionic nerve endings (figure 16).

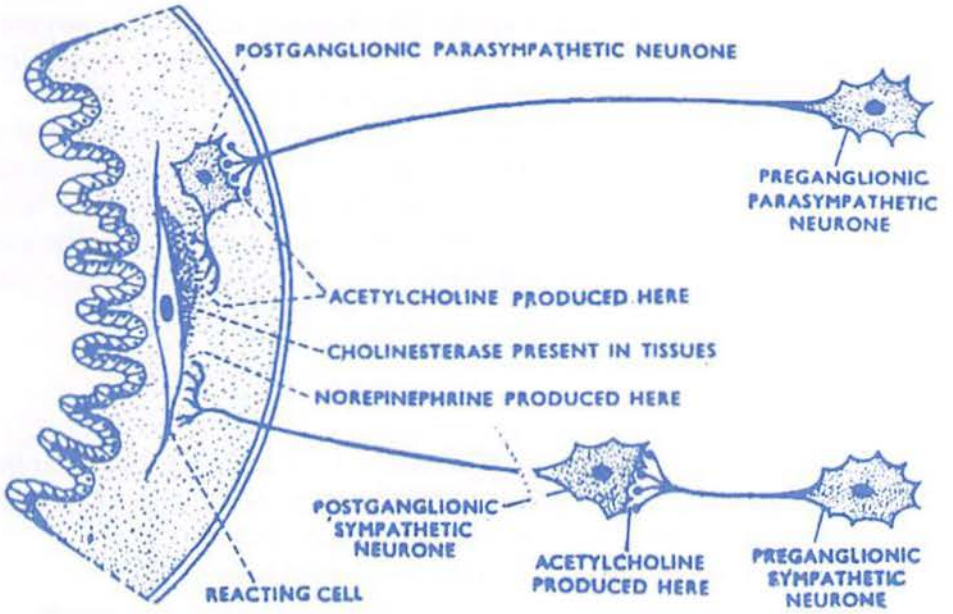


Figure 16 : Chemical transmitters released by autonomic nerves (note that symp. pregang. neurons relay away from the effector organ while parasymp. pregang. neurons relay in its wall).

The parasympatholytic drugs or Anti-acetylcholine drugs (= ac. ch. blockers, antagonists or inhibitors)

These drugs ***do not prevent the synthesis or release of ac.ch.*** from nerve endings but ***only antagonize its actions*** by either **(1) Competitive inhibition** i.e. the drug occupies the cholinergic receptors, so the released ac.ch. becomes unable to bind to them **(2) Persistent depolarization** i.e. the drug strongly depolarizes the cholinergic rreceptors, so they cannot be excited by the released ac.ch.. They are divided into **3 groups** :

(A) Blockers of the muscarine-like action

These drugs block the actions of ac.ch. at the parasympathetic and sympathetic cholinergic postganglionic nerve endings only (by ***blocking***

The muscarinic receptors). They include mainly *the belladonna alkaloids* e.g. ***atropine, homatropine, hyoscine and scopolamine***.

These drugs act by the ***competitive inhibition mechanism,*** and they do not affect the nicotinic receptors in the autonomic ganglia or motor end plates.

Clinical use : Atropine is used to ***dilate the pupils*** (for examination of the fundus of the eye), ***to relieve spasm*** (e.g. renal or intestinal colic) and to ***prevent bronchial secretions*** (so it is given before surgical operations).

** Although the oculomotor nerve excites both the constrictor pupillae and most of the external ocular muscles (by releasing ac. ch.), yet ***atropine blocks its action only in the former site*** (because it contains muscarinic receptors) but not in the latter (because it contains nicotinic receptors).

** *Acetylcholine injection can raise the arterial blood pressure* if given ***after injection of atropine***. In this case, the muscarinic (parasympathetic) actions of ac. ch. are blocked (thus no V.D. occurs) while its nicotinic actions are not affected, leading to *stimulation of the sympathetic ganglia and secretion of catecholamines from the adrenal medullae,* and both effects cause V.C. which raises the arterial blood pressure.

(B) Ganglion blockers

These drugs block the nicotine-like actions of ac.ch. ***mainly at the autonomic ganglia*** (thus preventing transmission of impulses from the preganglionic to the postganglionic neurons). They include :

(1) ***Hexamethonium,*** which acts by persistent depolarization.

(2) ***Arfonad*** (trimethaphan), which acts by competitive inhibition.

** ***Large doses of ac.ch. or nicotine*** also block conduction of impulses in the autonomic ganglia by persistent depolarization.

Clinical use : Ganglion blockers are used in treatment of ***hypertension*** to block conduction in sympathetic ganglia (which decreases the V.C. tone).

(C) Neuromuscular blockers

These drugs also block the nicotine-like actions of ac.ch. but ***mainly at the motor end plates*** (thus inhibiting neuromuscular transmission). They include mainly **curare (tubocurarine)** and some other related drugs (e.g. ***Flaxedil***), which act by ***competitive inhibition***.

Clinical use : These drugs are used as ***muscle relaxants*** during surgical operations. *Curare was used by* ***Red Indians*** *to paralyze their victims* (and in large doses, it may be fatal due to paralysis of the respiratory muscles).

** Both the neuromuscular and ganglion blockers prevent the nicotine-like actions of ac.ch., but ***each group of these drugs acts specifically at one site and minimally affects the other*** (indicating that the nicotinic receptors at the 2 sites are not identical).

The parasympathomimetic drugs

These drugs are divided into **2 main groups :**

(A) Drugs that directly stimulate the muscarinic cholinergic receptors : These include ac.ch. derivatives that are not rapidly hydrolyzed by the cholinesterase enzyme e.g. ***metacholine and pilocarpine***.

(B) Drugs that inhibit the cholinesterase enzyme (= *anticholinesterase drugs*) : These drugs *indirectly cause parasympathetic effects*, since they act by *preserving the released ac.ch.*, and they are **2 types :**

(1) Those having **a reversible effect** i.e their actions are temporary e.g. ***eserine*** (= ***physostigmine***) ***and prostigmine*** (= ***neostigmine***).

(2) Those having **an irreversible effect** i.e. their actions last for long periods e.g. ***parathion*** (an insecticide) and ***D.F.P.*** (diisopropyl-fluorophosphate) which is a toxic nerve gas.

Difference between eserine and prostigmine

Eserine blocks the cholinesterase enzyme ***allover the body*** while ***prostigmine blocks this enzyme mainly at the motor end plates***

Clinical uses of the anticholinesterase drugs

(1) ***Eserine is used only as eye drops to induce pupilloconstriction*** for treatment of an eye disease called ***glaucoma*** (refer to special senses).

(2) Myasthenia gravis : This is a disease characterized by severe muscle weakness and easy fatigability. It is ***an autoimmune disease*** in which antibodies that attack the muscular nicotinic receptors are formed. It is treated by ***prostigmine***, which leads to local accumulation of ac.ch. at the motor end plates (thus helping initiation of muscle contraction).

** ***Eserine is not used in the treatment of myasthenia*** because it produces (besides muscle contraction) ***dangerous parasympathetic effects*** e.g. ***hypotension*** due to V.D. and bradycardia, in addition to ***other undesirable effects*** e.g. excessive salivation, erection, defecation and micturition.

** ***The antagonist of eserine is atropine*** and the ***antagonist of atropine is either ac.ch. or eserine***.

** *Stimulation of the pelvic nerve can produce bradycardia* **if** *preceded by injection of eserine* because the cholinesterase enzyme will be blocked, so the ac. ch. liberated as a result of pelvic nerve stimulation is preserved and escapes to the blood, leading to bradycardia on reaching the heart.

General functions of the parasympathetic nervous system

The parasympathetic nervous system exerts a continuous effect (= tone) on the eyes and heart (in the latter, it is called the ***vagal tone***). Its actions are ***localized and of short duration*** and its effects are mostly ***anabolic***. It acts mainly during ***rest and sleep*** (not in emergency conditions as in case of the sympathetic nervous system) and the ***sacral division controls micturition, defecation and erection***.

CONTROL OF THE AUTONOMIC NERVOUS SYSTEM

The lateral horn cells and brain stem nuclei from which the autonomic preganglionic neurons arise are controlled both reflexly i.e. by impulses arriving along afferent neurons (figure 4) as well as by descending impulses from certain higher centres in the nervous system (figure 5 A).

(A) Reflex control of autonomic functions

(1) Spinal autonomic reflexes

These produce responses by stimulating the spinal autonomic centres (the lateral horn cells). Common examples include the following :

(a) ***The micturition, defecation and erection reflexes*** *:* Distention of either the urinary bladder or rectum, or irritation of the penis stimulate certain receptors in these organs, which discharge impulses along afferent nerves to the sacral region of the spinal cord, resulting in micturition, defecation or erection (depending on the stimulated organ) via the sacral parasympathetic outflow.

(b) ***The peritoneal-visceral reflex*** **:** Peritoneal irritation leads to discharge of impulses along afferent nerves to the spinal cord, where they stimulate the sympathetic centres (in the lateral horn cells) which discharge efferent impulses via the splanchnic nerves, resulting in relaxation of the visceral walls. This condition is known as ***paralytic or adynamic ileus***, and is commonly observed following major abdominal operations and in cases of peritonitis (refer to digestion).

(2) Brain stem autonomic reflexes

These produce responses by stimulating the ***cranial parasympathetic centres in the brain stem***. Common examples include the following :

(a) ***Reflex salivary, gastric and pancreatic secretion*** **:** Introduction of food in the mouth stimulates the taste and other receptors in the buccal cavity which discharge impulses along afferent nerves to the brain stem where they stimulate the salivary and dorsal vagus nuclei resulting in reflex salivary, gastric and pancreatic secretion. These responses are called ***unconditioned reflexes*** (refer to digestion, page 10)

(b) ***Reflex pupilloconstriction*** **:** On exposing the eyes to light (and also during accommodation to near vision), the photoreceptors in the retina are stimulated leading to discharge of impulses in afferent fibres of the optic nerve which stimulate the ***Edinger-Westphal nucleus*** in the midbrain (page 19) resulting in miosis (= pupilloconstriction). These reflexes are called the ***light and near reflexes*** *respectively* (refer to special senses).

(B) Higher control of autonomic functions

The higher centres that control autonomic functions include the ***reticular formation, the hypothalamus and certain areas in the cerebral cortex*** (*areas 6 and 8, the limbic lobe and prefrontal area*).

(1) The reticular formation

The reticular formation is a collection of nerve cells and fibres in the brain stem which contains many centres that control autonomic functions, specially the centres in the medulla oblongata that control **(a)** Gastro-intestinal functions e.g. the deglutition and vomiting centres **(b)** Cardio-vascular functions (the vasomotor and cardioinhibitory centres).

These centres control the lateral horn cells by discharging impulses via descending nerve fibres called the ***reticulospinal tract*** e.g. if the arterial blood pressure is lowered (as occurs in cases of severe hemo-rrhage) the vasomotor centre is activated and the descending impulses stimulate the sympathetic lateral horn cells leading to generalized V.C. in the body as well as heart acceleration, and such responses result in elevation of the arterial blood pressure towards the normal level.

(2) The hypothalamus

The ***anterior hypothalamic nuclei control parasympathetic functions while the posterior hypothalamic nuclei control sympathetic functions***. The hypothalamus exerts its effects ***through affecting the centres located in the reticular formation*** e.g. in certain emotions, impulses are discharged from the hypothalamus to the medulla oblongata where they stimulate the vasomotor centre leading to generalized V.C.and tachycardia (= increased heart rate) through stimulating the sympathetic nervous system. These effects are augmented by catecholamines released from the adrenal medullae, and result in marked rise of the arterial blood pressure.

(3) The cerebral cortex

This controls the autonomic centres in both the hypothalamus and reticular formation. Examples of the cortical controlon autonomic functions include the following :

(a) Cortical signals lead to V.D. in skeletal muscles on performing muscular exercise via the ***sympathetic V.D. system*** (page 14).

(b) Prolonged mental work stimulates the vasomotor centre and frequently leads to chronic hypertension.

(c) Cortical impulses increase the heart rate during certain emotions.

(d) Thinking of food induces salivation aas well as gastric and pancreatic secretion by cortical signals that stimulate the salivary and vagal nuclei in the brain stem. These responses are called ***conditioned reflexes*** (refer to digestion).

SECTION II

NERVE AND MUSCLE

THE NERVE

Nerves and muscles are studied together because both are excitable structures that conduct impulses, but the musclesalso contract.

Peripheral nerve trunks contain large number sof ***independent nerve fibres*** that may be either :

(1) ***Afferent*** **(= *sensory*)** ***nerve fibres*** **:** These transmit nerve impulses (or signals) from peripheral receptors to the nervous system.

(2) ***Efferent*** **(= *motor*)** ***nerye fibres*** **:** These transmit nerve impulses (or signals) from the nervous system to the effector organs.

PROPERTIES OF NERVES

(1) Excitability

This is the ability of living tissues to respond to various stimuli. It is an ***electric phenomenon,*** and the electric changes that accompany nerve excitation are called the ***action potential***. Such changes are very small and very rapid, so their magnitudes are measured in ***millivolts*** **(mV)** while their durations are measured in ***milliseconds*** **(msec)**. They are recorded by microelectrodes connected to either ***a galvanometer or a cathode ray oscilloscope*** **(CRO)**. The latter consists of a cathode emitting a beam of electrons which is directed to strike a screen (figure 17). This screen is covered with a fluorescent phosphorous substance that emits light when struck by the electrons. The potential changes in the nerve are picked up by the microelectrodes and amplified (by an electronic amplifier), then they are transmitted to the CRO where they are recorded as deflections of the electronic beam on its screen.

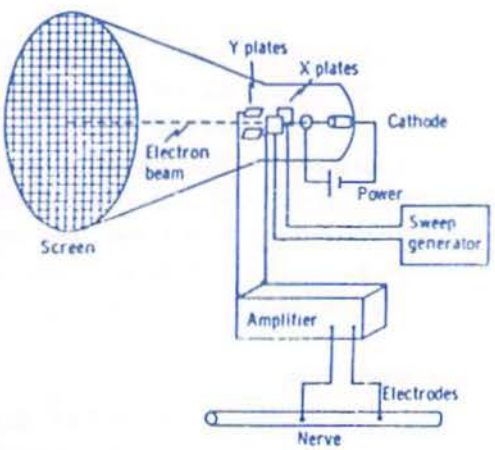


Figure 17 : The cathode ray oscilloscope (CRO).

The stimulus

A stimulus is a change in the environment around the nerve (or muscle) which may be either ***chemical, thermal, mechanical or electrical***. In laboratories, ***electrical stimuli are preferred*** because they can be accurately controlled (both in strength and duration) and, in addition, they leave the stimulated structures without damage. The following 2 types of electric currents can be used for stimulation of excitable tissues :

(a) The galvanic current : This is a ***constant*** (***or direct***) ***current*** (**D.C.**) which is obtained from a battery.

(b) The faradic current : This is an ***alternating current*** (**A.C.**) like the ***induction currents*** used in laboratories for nerve stimulation.

(2) Conductivity

The physicochemical change produced by various stimuli in the nerve is called the ***nerve impulse***. Such impulse is actively conducted along the nerve fibre and it can be conducted in ***both directions*** if the nerve was stimulated at its middle. However, in the body, each nerve conducts impulses in one direction only (motor nerves toward the effector organs and sensory nerves toward the nervous' system). Conduction in the normal direction is called ***orthodromic conduction***, but if it occurs in the opposite direction due to any cause, it will be called ***antidromic conduction***.

(3) All or none law (or rule)

This law states that ***"A threshold*** (= ***minimal***) ***stimulus produces a maximal response " i.e. a maximal action potential in nerve and muscle fibres and a maximal contraction in muscle fibres***. Therefore, *as long as other factors that affect excitability remain constant*, ***increasing the intensity of the stimulus above the threshold value produces no further increase in the action potential or muscle contraction***

The all or none law is **obeyed in the following structures :**

(a) *A single nerve fibre.*

(b) *A single skeletal muscle fibre and the motor unit* (page 51).

(c) *The cardiac muscle and some smooth muscles* (page 78) which act as one unit called ***syncytium*** (refer to circulation).

However, ***nerve trunks and whole skeletal muscles*** (which contain many fibres) ***do not obey the law***. This is because ***the threshold intensity for stimulation varies in the different types of nerve and muscle fibres*** (i.e. it is ***not equal***).*Therefore, if the intensity of stimulation is increased in these structures, the response will also increase till reaching a maximum.*

(4) Accommodation (or adaptation)

The nerve fibre adapts to stimulation by a constant current, so no response occurs during passage of the current, and it occurs only on the ***make*** (i.e. closing) and ***break*** (i.e. opening) of the electric circuit.

(5) Infatiguability

Nerve fibres are ***not fatigued by continuous stimulation*** (page 70).

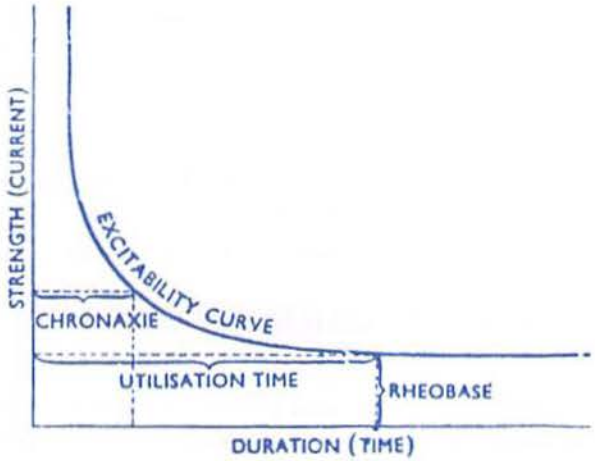


Figure 18 : The strength duration curve.

Factors that determine the effectiveness of stimuli

(1) Intensity (= strength) of the stimulus : Subthreshold stimuli produce only ***local responses*** that don't initiate action potentials (see later).

(2) Rate of increase in the intensity of stimuli : Subthreshold stimuli that are gradually increased produce a response only with a rapid increase in the intensity of stimuli. If the intensity is increased slowly, the nerve will not respond because of the property of accommodation (see above).

(3) Duration of stimulus (= duration of current flow) : The relation between the intensity of a stimulating current and the duration (time) of its flow necessary to set up an impulse is shown in the ***strength-duration curve*** (figure 18). From the curve, the following observations are noticed :

(a) Within limits, there is a ***reciprocal relationship between the current strength and the duration of flow required to produce an impulse***

(b) There is a ***minimal duration needed for excitation*** below which no excitation occurs whatever may be the strength of the stimulus.

(c) RHEOBASE : This is the ***minimal strength*** (***or threshold intensity***) ***of a galvanic current that can set up an impulse***. The time required for excitation when using the rheobase is called the ***utilization time***.

(d) CHRONAXIE : This is the duration of current flow required for excitation ***when using a strength equal to twice*** (***or double***) ***the rheobase***.

Use of Chronaxie **:** The chronaxie is a good index for ***the degree of excitability*** (the shorter the chronaxie, the greater the excitability and vice

versa) and its measurement can be used to ***compare the excitability of different tissues, or that of the same tissue under different conditions***.

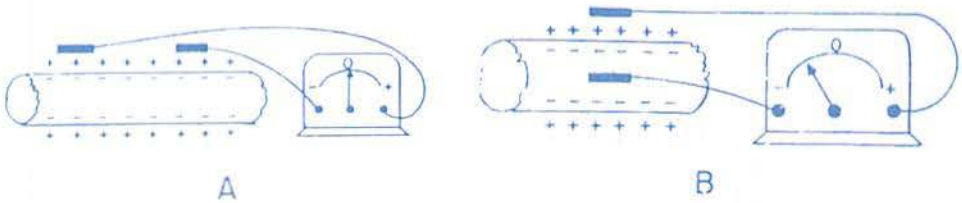


Figure 19 : The resting membrane potential.The outer surface of the nerve fibre is isoelectric(A) and a potential difference (-70 mV) is recorded when one of the microelectrodes is inserted into the nerve fibre (B)

THE RESTING MEMBRANE POTENTIAL (RMP)

In resting nerves, the outer surfaces are + ve and the inner surfaces are -ve, with a potential difference about **-70 mV**. This is called the resting membrane potential, and the membrane is said to be in the ***polarized state***. For this reason, if 2 microelectrodes connected to a galvanometer are placed on the outer surface of a nerve, no potential is recorded (figure 19 A), but when one of the microelectrodes is inserted inside the nerve, a potential difference of about -70 mV will be recorded (figure 19 B).

The resting membrane potential is present not only in nerves but also in muscle fibres and *almost all cells in the body*, with the inside negative relative to the outside (ranging in different tissues from **-9 to -100 mV**).

Cause of the resting membrane potential (RMP)

Outside the cell membranes, there are mainly Na^+, Cl^- and HCO_3^- while inside the cell there are mainly K^+ and organic protein anions (which are negatively charged). The RMP is due to an ***unequal distribution of ions on both sides of the cell membranes*** with relatively excess cations outside and excess anions inside, which is produced as a result of 2 main factors **(a)** ***Selective permeability of cell membranes*** **(b)** ***The Na^+ - K^+ pump***.

(A) Selective permeability of cell membranes

The cell membranes are ***impermeable to the intracellular protein anions*** (because of their large size), which are thus ***kept inside producing a great negative charge***. On the other hand, other anions (Cl^- and HCO_3^-) pass easily due to their small sizes. These membranes are also fairly permeable to K^+ but less permeable to Na^+ (*their permeability to K^+ is 50-100 times greater than their permeability to Na^+*).

The diffusion of ions across cell membranes occurs along both their concentration and electrical gradients. In addition, some ion channels are ***voltage-gated*** (i.e. controlled by the present potential), while others are ***ligand-gated*** (i.e. controlled by certain chemical substances).

** The direction of the concentration and electrical gradients of Na^+ is inwards, so ***Na^+ ions tend to diffuse inside the cells***, but this is limited due to the low permeability of the cell membranes to Na^+. Therefore, Na^+ ions accumulate outside the membranes, helped by the Na^+-K^+ pump (see below) producing a considerable positive charge.

** On the other hand, the concentration gradient of K^+ is directed outwards, so ***K^+ ions tend to diffuse outside the cells***. However, this is limited because **(a)** The electrical gradient is directed inwards **(b)** The +ve charge on the outside of the membranes repels K^+ ions inwards **(c)** The sodium-potassium pump actively drives K^+ ions inwards (see below).

** In case of Cl^- and HCO_3^-, the concentration gradient is directed inwards, so these anions tend to diffuse into the cells. However, this is limited because the interior of the cells has a great -ve charge, and accordingly, they are expelled out of the cell along this electrical gradient.

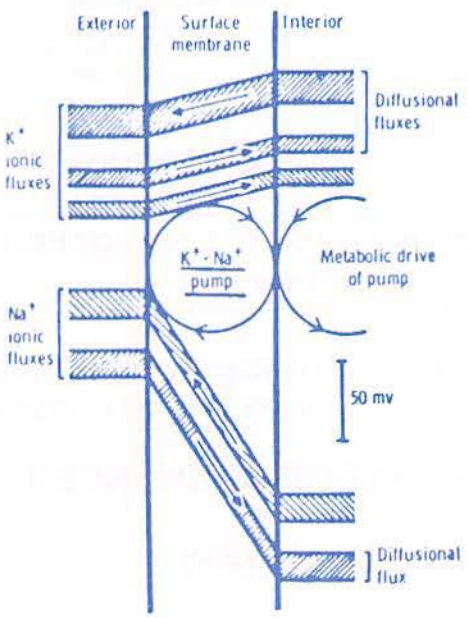


Figure 20 : Na^+ and K^+ fluxes (movements) through the resting nerve membrane, showing the Na^+ - K^+ pump. The diffusional fluxes are due to passive diffusion.

(B) The sodium-potassium pump

In the resting condition, Na^+ ions tend to diffuse into the nerve fibres as described above. However, they are not allowed to accumulate

inside the nerves. They are pumped outwards by an active process (since it occurs against both concentration and electrical gradients) which needs energy (that is provided from breakdown of ATP by activity of the enzyme Na^+ - K^+ ATPase). The outward pumping of Na^+ ions is coupled with active transport of K^+ ions inwards, so this process is called the ***sodium-potassium pump*** (figure 20). It is an ***electrogenic pump*** that helps to maintain the resting membrane potential since it has a coupling ratio of 2/3 (i.e. it ***pumps 3 Na^+ out of the cell and transports only 2 K^+ into the cell***), which produces a net movement of +ve charges out of the cell.

** *At equilibrium, and as a result of the selective permeability of the cell membranes and the Na^+ - K^+ pump, the outer surfaces of nerve fibres will be +vely charged* (***mainly due to Na^+***) *while their inner surfaces will be -vely charged* (*mainly* ***due to protein***), *producing a potential difference of about -70 mV* (*which is the resting membrane potential*).

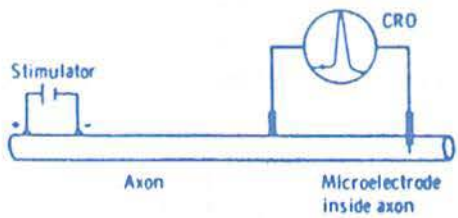


Figure 21 : Recording of the action potential.

Changes that accompany propagation of a nerve impulse

The propagation of a nerve impulse is accompanied by 4 changes (electric, excitability, metabolic and thermal changes).

(1) ELECTRIC CHANGES

THE ACTION POTENTIAL (AP)

The A.P. refers to the changes in potential that occur in excitable tissues when stimulated. In case of nerve fibres, it is transmitted as a ***self-propagated disturbance known as the nerve impulse***. It can be recorded by the CRO through 2 microelectrodes, one is inserted inside the nerve and the other is placed on its outer surface (figure 21). Stimulating the nerve (by an electric stimulator) is marked by a ***stimulus artifact***, which is due to *current leakage from the stimulating electrode to the recording (external) electrode*. This is followed by a ***latent period*** (which is an isopotential

interval representing the time taken by the impulse to reach the recording electrode) after which the AP is recorded. The AP consists of 2 main stages (called ***depolarization and repolarization***) that are followed by 2 other stages known as ***after-depolarization and after-hyperpolarization*** (figure 22).

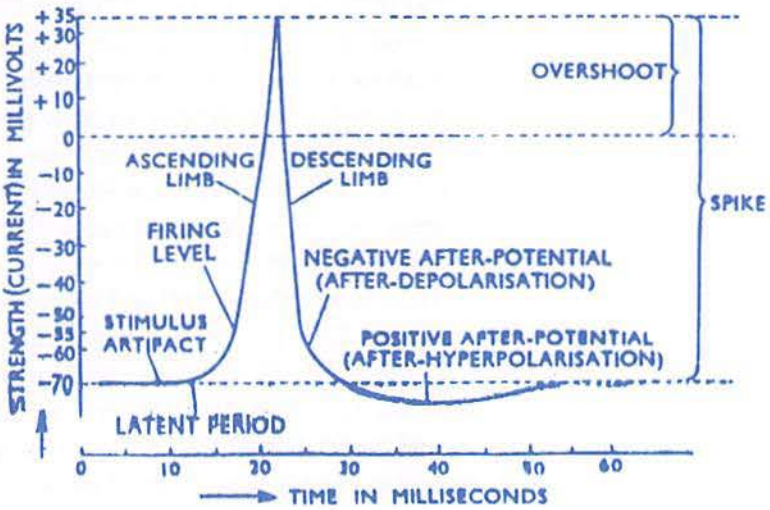


Figure 22 : Various stages of the action potential (A.P.).

(A) Depolarization (DP)

This is ***loss of the normal resting polarized state*** of the membrane (i.e. loss of the normal potential difference between the inner and outer surfaces of the membrane). It is recorded as a rise of the membrane potential in the positive direction from -70 mV towards the isopotential line (zero potential), producing **the ascending limb of the A.P.** (figure 22). Such process occurs in steps as follows :

(1) DP develops slowly, but after an initial 15 mV of DP (i.e. when the membrane potential becomes about **-55 mV**), the rate of DP suddenly increases (so this point is called the ***firing level***).

(2) DP then proceeds rapidly till the resting membrane potential is lost (i.e. the potential difference between both sides of the membrane becomes zero), after which the membrane potential often reaches ***+35 mV*** (indicating that the inner surface of the membrane becomes positive relative to the outer surface). Accordingly, this change is called ***overshoot or reversal of polarity***, and it results in an A.P. having a magnitude of. **105 mV** (from -70 to +35 mV).

(B) Repolarization (RP)

This is restoration of the normal resting polarized state of the membrane. It is recorded as a fall of the membrane potential in the negative direction from + 35 mV to -70 mV, producing **the descending limb of the A.P.** (figure 22). Such process occurs in steps as follows :

(1) RP proceeds immediately and rapidly after the overshoot is reached.

(2) When RP is 70-80 % completed, its rate decreases for about ***4 msec***. This stage is called ***after-depolarization*** (***or negative afterpotential***).

(3) After RP is completed, the membrane potential ***overshoots to the negative side*** (by about 1-2 mV) leading to *hyperpolarization of the membrane* This stage is called ***after-hyperpolarization*** (***or positive afterpotential***). It lasts about ***40 msec*** but its magnitude gradually declines till the normal resting membrane potential is restored (figures 22 and 23).

** The recorded AP is called ***monophasic AP*** and its components are diagrammatically shown in figure 22. However, the *actual tracing recorded by the CRO* is shown in figure 23, in which the rise of the AP is so rapid that it does not clearly show the change in DP rate at the firing level. Because of the sharp rise and rapid fall of the AP, it is commonly called the ***spike potential*** (***or the spike***), and it lasts about ***2 msec***.

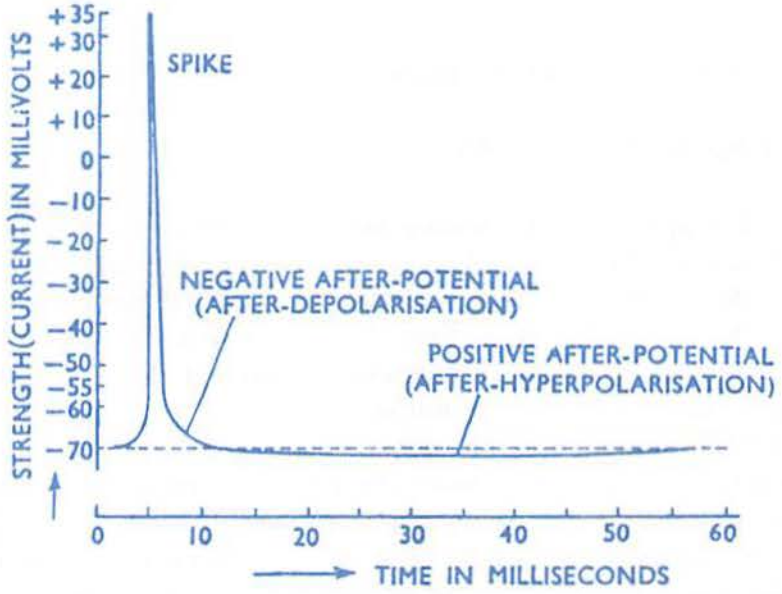


Figure 23 : The action potential as recorded by the CRO.

Ionic basis (or mechanisms) of DP and RP

(A) Depolarization (DP) and overshoot

The initial slow DP is produced by the stimulating current itself as follows : Stimulating currents are ***cathodal in nature*** which add negative

charges outside the nerve membrane. Thus the potential difference between both sides of the membrane is decreased and the membrane potential becomes less -ve than at the resting state. This is called **electrotonic DP**.

On the other hand, the rapid phase of DP and the overshoot are produced by ***an increase in Na^+ influx*** (= entrance) into the nerve fibre as a result of ***increased Na^+ conductance of the nerve membrane*** (figure 24). which occurs secondary to ***marked increase in the Na^+ permeability*** of the membrane through opening of specific ***Na^+ channels in the membrane,*** which occurs as follows : Each Na^+ channel has an ***activation gate*** at the outer surface of the membrane and an ***inactivation gate*** at its inner surface, and the membrane Na^+ conductance (and consequently the Na^+ influx) is ***increased only when both gates are opened.***

In the resting state, only the inactivation gates are open so the membrane permeability to Na^+ is low. However ***when the nerve is stimulated, the Na^+ activation gates also open*** thus the membrane permeability and conductance to Na^+ as well as Na^+ influx are markedly increased.

Opening of the Na^+ activation gates is ***voltage-dependent***. They start to open when the initial electrotonic DP becomes 7 mV. This allows Na^+ influx, which further decreases the membrane polarity leading to opening of more gates. This results in more Na^+ influx and more decrease of the membrane polarity, which leads to opening of more and more gates and more Na^+ influx. Such process continues in the form of a ***vicious circle*** (***i.e. by a positive feedback mechanism***) till all gates open.

The *rate of opening of the Na^+ activation gates is slow* between 7 and 15 mV of DP (i.e.. till a membrane potential of about -55 mV) leading to slow DP. However, after 15 mV of DP, the rate of opening of these gates suddenly increases leading to much acceleration of DP (***the firing level***).

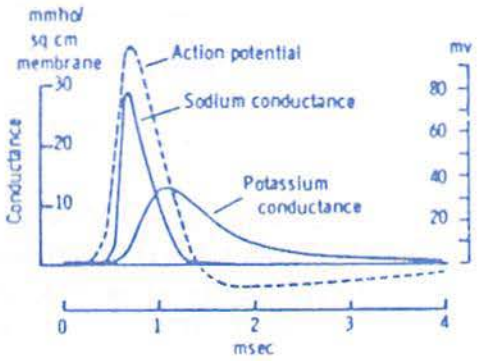


Figure 24: Changes in Na^+ and K^+ conductance during the action potential

(B) Repolarization (RP) and after-potentials

RP of the membrane takes place rapidly after DP as a result of :

(1) Stoppage of Na^+ influx due to **(a)** *Closure of the Na^+ inactivation gates* **(b)** *Reversal of the direction of electrical gradient for Na^+* (which

becomes from inside toward the outside of the membrane)

(2) K^+ efflux (exit) from the nerve fibre : This occurs through specific K^+ channels that contain ***a single gate located toward the inside of the membrane***. The decrease in membrane polarity during DP leads to opening of the K^+ gates, thus the K^+ conductance is markedly increased and K^+ efflux occurs. However, this process is *slower* than opening of the Na^+ channels so the increase in K^+ conductance is slightly delayed (figure 24).

The **negative afterpotential stage** is due to slowing of the rate of K^+ efflux, while the **positive afterpotential stage** is due to slow return of the K^+ channels to the closed state (which allowsprolonged K^+ efflux).

The slow opening and delayed closure of the K^+ channels may explain the phenomenon of ***accommodation*** that occurs in nerves (page 31).

Following the AP , the resting Na^+ and K^+ ionic gradients (i.e. their normal distribution) across the nerve membrane are restored by the action of the Na^+- K^+ pump (figure 25 d).

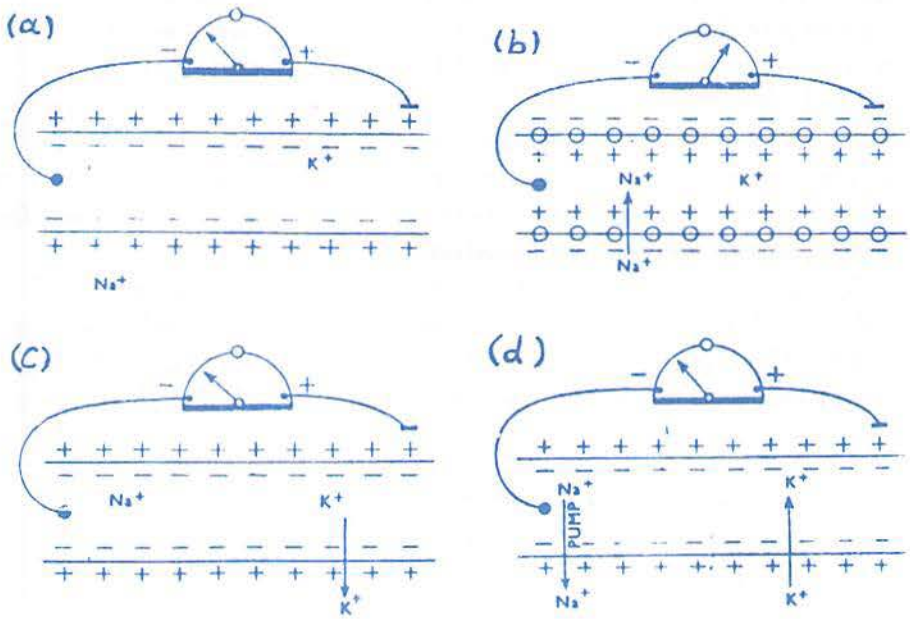


Figure 25 : Ionic changes during various stages of the action potential. **(a)** Resting membrane potential (-70 mV) **(b)** Depolarization and overshoot (due to Na^+ influx) **(c)** Repolarization (due to K^+ efflux) **(d)** Restoration of the resting potential (due to Na^+ - K^+ pump).

Role of Ca^{2+} in nerve excitation

Normally, both the concentration and electrical gradients for Ca^{2+} are directed inwards, and the Ca^{2+} conductance increases during nerve excitation leading to Ca^{2+} influx. Therefore, ***Ca^{2+} contributes to DP*** (and in some invertebrates, it is primarily responsible for the AP). Ca^{2+} influx

occurs via *voltage-gated Ca^{2+} channels* which are also slightly permeable to Na^+ (so they are called ***Ca^{2+}- Na^+ channels***). However, they are very slow to become activated, so they are also called ***slow channels*** (in contrast to the voltage-gated Na^+ channels which are called ***fast channels***).

The extracellular Ca^{2+} concentration also ***affects nerve excitability***. Its ***decrease increases the excitability*** while its ***increase decreases the excitability*** and stabilizes the nerve membrane (page 45).

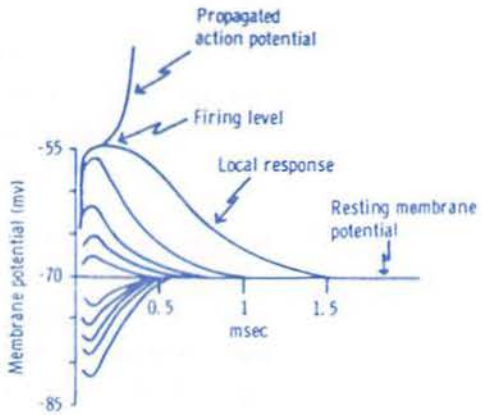


Figure 26 : Eiectrotonic potentials and the local response.Membrane polarities more than the resting membrane potential are catelectrotonic while those less than the resting membrane potential are anelectrotonic.

Electrotonic potentials (ETPs) and the local response

ETPs are ***localized potential changes*** that occur in nerves when stimulated by ***subthreshold constant currents***. Such currents are obtained from batteries and either the –ve electrode (= cathode) or the + ve electrode (= anode) can be used for stimulation. Accordingly, there are 2 types of the ETPs, both of which are ***passive changes in the membrane polarization*** (i.e. produced by addition or subtraction of charges through the stimulating electrode) that decay (i.e. disappear) gradually (figure 26). These include :

(A) Anelectrotonic potential (or anelectrotonus)

This is the potential change that occurs when using anodal (i.e. +ve) currents for stimulation. It is a state of ***hyperpolarization*** caused by addition of +ve charges at the outer surface of the nerve membrane, and the ***magnitude of the potential change is proportionate to the strength of the stimulus***. It is associated with ***a decrease of excitability of the nerve*** and with strong anodal currents, the nerve excitability may be completely lost (= ***anodal block***). This is because it takes the membrane potential ***away from the firing level*** (which inhibits discharge of impulses).

(B) Catelectrotonic potential (or catelectrotonus)

This is the potential change that occurs when using cathodal (i.e. -ve) currents for stimulation.It is a state of ***partial DP*** caused by addition of -ve charges at the outer surface of the nerve membrane. It is associated with an ***increase of excitability*** of the nerve, and the ***magnitude of the potential change varies with the strength of the stimulating current*** as follows :

(1) When using weak currents that produce up to 7 mV of DP, the magnitude of the potential change is ***proportionate to the strength of the stimulus***.

(2) When using stronger currents that produce more than 7 mV (up to 15 mV) of DP, the magnitude of the potential change is ***greater than expected***. This exaggerated potential change is called the **local response** and is due to activation of the voltage-gated Na^+ channels and start of Na^+ influx.

However, in both conditions the decrease of the membrane polarity also leads to an increase in K^+ efflux which repolarizes the membrane and restores the resting membrane potential, so the resulting catelectrotonus decays gradually and ***no action potentials are produced*** (figure 26).

On the other hand, when using cathodal currents of threshold or suprathreshold intensities (i.e. great enough to produce more than 15 mV of DP), the threshold for excitation (i.e. **the firing level**) is reached. This is normally a membrane potential of about -55 mV, at which the depolarization force (i.e. Na^+ influx) becomes stronger than the repolarization force, leading to production of a propagated action potential (figure 26).

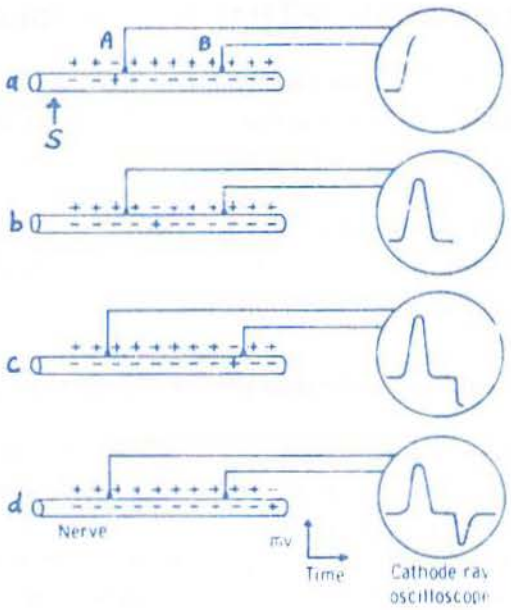


Figure 27 : The biphasic action potential. S = Stimulus.

THE BIPHASIC ACTION POTENTIAL

This is recorded when 2 microelectrodes connected to a CRO are placed ***at 2 points*** (***A and B***) on the outer surface of a nerve fibre, and a stimulus is applied beyond them (figure 27). It consists of the following phases :

(1) At first, there is no potential difference between the 2 points because both are +vely charged (i.e. both are isoelectric).

(2) When the impulse reaches point A, it will be depolarized, becoming -ve relative to point B, thus an upward deflection is recorded by the CRO (figure 27 a).

(3) When the impulse leaves point A, it will be repolarized (developing a +ve charge), so the 2 points become isoelectric again and the deflection returns back to the base line (figure 27 b).

(4) When the impulse reaches point B, it will be depolarized, becoming -ve relative to point A, so a deflection is recorded but in the opposite direction i.e. downwards (figure 27 c).

(5) When the impulse leaves point B, it will be repolarized (developing a +ve charge), so the 2 points become isoelectric again and the deflection returns back again to the base line (figure 27 d).

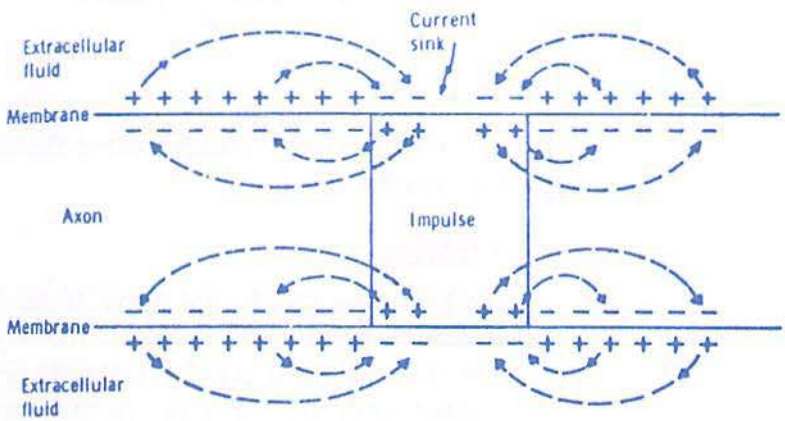


Figure 28 : Conduction of nerve impulses in unmyelinated nerve fibres.

MECHANISM OF NERVE IMPULSE CONDUCTION

(A) In unmyelinated nerve fibres

Nerve impulses are propagated along unmyelinated nerve fibres in the form of **a wave of APs** (figure 28). The initial stimulus causes reversal of polarity and an AP at the point of stimulation (so the outer surface of the nerve membrane at that point becomes negatively charged). ***Local circular currents*** flow between the activated point and the neighbouring

inactive areas of the nerve membrane. +ve charges from the inactive areas flow into the initial area of negativity produced by the AP (= ***area of current sink***). This decreases the polarity at the inactive areas (= ***electrotonic depolarization***) which produces an AP initiating on reaching the firing level. The latter areas, in turn, electrotonically depolarize the membrane in front of it through local circular currents, and this sequence of events moves regularly along the nerve fibre to its end.

Therefore, the nerve impulse is ***self-propagated***, and once it leaves a point, this point will soon repolarize (thus ***a repolarization wave starts after the depolarization wave and is propagated in the same direction***).

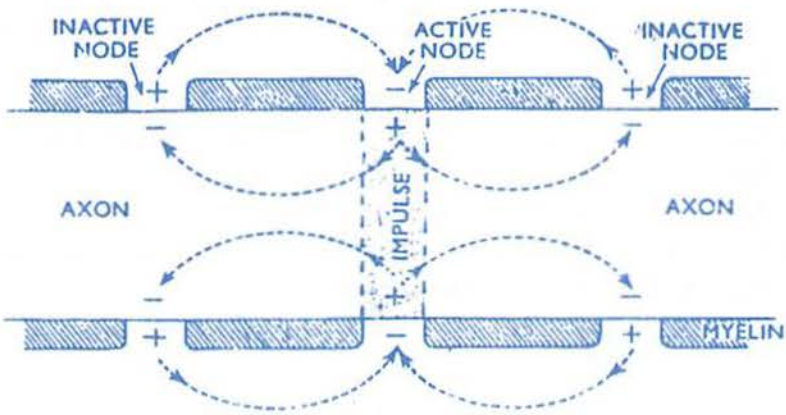


Figure 29 : Conduction of nerve impulses in myelinated nerve fibres (= **saltatory conduction**).

(B) In myelinated nerve fibres

Nerve impulses are propagated along myelinated nerve fibres by a special mechanism called the **saltatory conduction** (figure 29). Myelin surrounds the nerve axon and is interrupted at regular intervals at the ***nodes of Ranvier***. It is an **insulator** to current flow (in contrast to the nodes of Ranvier, which easily permit current flow because of their high permeability to Na^+).

Circular currents also flow in myelinated nerve fibres, but the +ve charges jump from the inactive nodes to the area of current sink at the active node (bypassing the myelin segments because of their insulator effect). This leads to electrotonic depolarization and production of an AP at the inactive nodes, which in turn activates the neighbouring nodes. This jumping of DP from node to node is called ***saltatory conduction***, and it results in **(a)** ***Increasing the velocity of conduction*** **(b)** ***Conservation of energy*** (because excitation occurs only in the nodes and not allover the nerve membrane).

(2) EXCITABILITY CHANGES

During propagation of a nerve impulse (i.e. during an AP), the excitability of nerve fibres passes in the following phases (figure 30) :

(1) Absolute refractory period (ARP) : During this period, the nerve is ***completely inexcitable***, thus no stimulus can excite it whatever its strength. It corresponds to the ascending limb of the AP from the time the firing level is reached (i.e. during DP and overshoot) and upper part of the descending limb (until RP is about 1/3 complete).

(2) Relative refractory period (RRP) : During this period, nerve excitability is only ***partially recovered***, thus stronger stimuli than normal are required for excitation. It corresponds to the remaining part of the descending limb of the AP till the start of after-depolarization (i.e. during the later 2/3 of RP).

(3) Supernormal phase (or period) : During this period, nerve ***excitability is increased***, thus weaker stimuli than normal can excite the nerve. It corresponds to the period of ***after-depolarization***.

(4) Subnormal phase period (or period) : During this period, nerve ***excitability is decreased***, thus stronger stimuli than normal are required for excitation. It corresponds to the period of ***afler-hyperpolarjzation***.

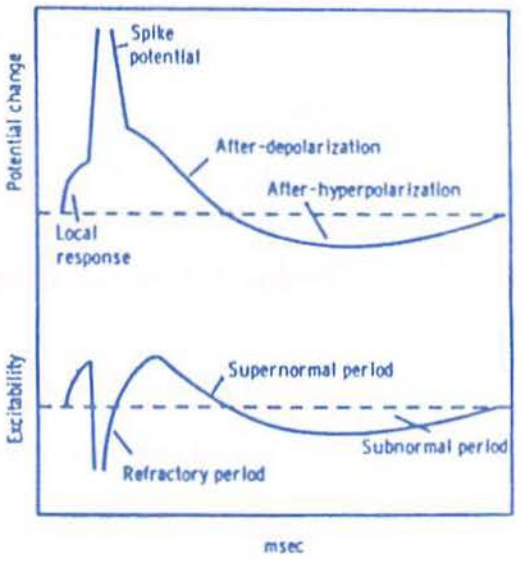


Figure 30 : The excitability changes in a nerve fibre during propagation of an impulse (i.e. during the action potential).

Factors that affect nerve excitability

(1) Temperature : Cooling decreases nerve excitability while warming increases it.

(2) Pressure : Mechanical pressure on a nerve reduces its excitability.

(3) Blood supply : Nerve excitability is decreased in cases of ischemia.

(4) Oxygen supply : O_2 lack decreases nerve excitability.

(5) H^+ concentration : Alkalinity increases while acidity decreases the excitability of nerves.

(6) Electrotonic potentials : Catelectrotonus increases while anelectrotonus decreases the excitability of nerves (page 40)..

(7) Chemicals : Nerve excitability is decreased by excess CO_2 and alcohol as well as by anesthetic drugs e.g.ether, chloroform and novocaine.

(8) Electrolytes : The concentrations of Na^+, K^+ and Ca^{2+} in the extracellular fluid affect nerve excitability as follows :

(A) Ionic changes that increase nerve excitability

1- Decreased Ca^{2+} concentration : This increases the membrane permeability to Na^+ and decreases the amount of DP necessary to initiate the changes in Na^+ and K^+ conductances that produce the AP (page 40).

2- Increased Na^+ concentration : This facilitates the process of DP.

3- Increased K^+ concentration : This favours K^+ influx which leads to DP, thus the nerve excitability will increase.

(B) Ionic changes that decrease nerve excitability

1- Increased Ca^{2+} concentration : This decreases the membrane permeability to Na^+ and increases the amount of DP necessary to initiate the changes in Na^+ and K^+ conductances that produce the AP (page 40).

2- Decreased Na^+ concentration : This decreases nerve excitability by delaying the process of DP.

3- Decreased K^+ concentration : This favours K^+ efflux which leads to hyperpolarization, thus the nerve excitability will decrease.

Methods of producing nerve block

Propagation of impulses by nerves can be blocked (i.e. prevented) by one of the following methods :

(1) Physical methods e.g. application of cold or a strong anelectrotonus (= ***anodal block***, page 40).

(2) Mechanical methods (e.g. application of pressure on the nerve).

(3) Chemical methods : These include **(a)** The ionic changes that decrease nerve excitability i.e. increased Ca^{2+} and decreased Na^+ or K^+ concentration in the extracellular fluid (see above) **(b)** Use of certain chemical substances known as the **membrane stabilizers** which include mainly ***the local anesthetic drugs*** (e.g. cocaine and novocaine): These drugs markedly decrease the membrane permeability to Na^+ (by preventing opening of the Na^+ channel activation gates), so the depolarization process is inhibited and nerve impulses fail to be produced.

(3) METABOLIC CHANGES

The metabolic processes that occur in nerves are generally similar to those occurring in muscles (page 58), and they involve O_2 consumption and ATP breakdown. In resting nerves, they occur at a low rate (mainly to maintain the polarized state) but they are much increased during transmission of nerve impulses.

The breakdown of ATP supplies the energy required for the sodium-potassium pump and nerve impulse propagation. It is resynthesized by energy derived from breakdown of glycogen (which leads to formation of lactic acid). Nerve fibres are also rich in vitamin B_1 which is necessary for their metabolic activities.

(4) THERMAL CHANGES

Resting nerves liberate little heat as a result of their low metabolic rate. However, during nerve impulse transmission the heat production by nerves is markedly increased, and is liberated in the following 2 stages :

(1) Initial heat : This coincides with ***propagation of the spike*** (i.e. during ionic migration), and it is due to anaerobic breakdown of ATP.

(2) Recovery (delayed) heat : *This* ***follows propagation of the spike,*** and it is due to ***aerobic reactions*** that liberate the energy required for ATP resynthesis. It continues for a relatively long time, and is about 30 times as much as the initial heat.

Effect of stimulation of peripheral (mixed) nerves

Peripheral nerves are mixed nerves since they contain different types of nerve fibres (see below), so the AP recorded from these nerves represents an ***algebraic sum of many APs*** (figure 31). Also, the excitability of these nerve fibres are variable, so the following effects are obtained on stimulating a peripheral nerve, ***depending on the intensity of the stimuli*** :

(1) Subthreshold (= subminimal) stimuli fail to excite any of the nerve fibres, so no potential changes will be recorded.

(2) Threshold (= minimal) stimuli excite only the nerve fibres that have the highest excitability, resulting in a small potential change.

(3) Supraminimal stimuli excite a greater number of nerve fibres, so a larger potential change will be recorded.

(4) Maximal stimuli excite all nerve fibres, resulting in a maximal potential change.

(5) Supramaximal stimuli produce no further increase in the potential change recorded by the maximal stimuli, because each nerve fibre obeys the ***all or none law*** (page 31).

Types of mammalian nerve fibres

The mammalian nerve fibres are classified ***according to their diameters*** into the following types :

(1) Group A nerve fibres : These have the largest diameters (3-20 microns) and the highest speeds of conduction (15-120 meters / second). They are further subdivided into ***alpha, beta, gamma & delta nerve fibres***. An example of this group is the ***somatic nerve fibres that transmit motor impulses & deep sensations***. They are ***most sensitive to pressure*** (i.e. the conduction of impulses in these nerves can be readily blocked by pressure). The average duration of spike in these nerve fibres is ***0.5 millisecond***

(2) Group B nerve fibres : These have smaller diameters (1.3-3 microns) and moderate speeds of conduction (3-15 meters / second). An example of this group is the ***myelinated preganglionic autonomic nerves***. They are ***most sensitive to O_2 lack***. The average duration of spike in these nerve fibres is ***1.2 millisecond***.

(3) Group C nerve fibres : These have the smallest diameters (0.3-1.3 microns) and the slowest speeds of conduction (0.5-3 meters /second). An example of this group is the ***unmyelinated postganglionic autonomic nerves***. They are ***most sensitive to local anesthetic drugs*** (see above). The average duration of spike in these nerve fibres is ***2 milliseconds***.

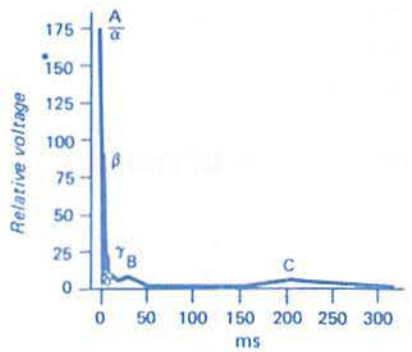


Figure 31 : Compound action potential recorded from a peripheral nerve

The compound action potential (cAP)

This is the AP recorded from peripheral nerves when stimulated by ***maximal stimuli***. These nerves contain different types of nerve fibres that ***vary in their speeds of conduction*** ; ***the thicker the nerve fibre, the more rapid is its rate of conduction of nerve impulses and vice versa*** (see above). Thus, the activity in fast-conducting nerve fibres arrives at the recording electrode earlier than the activity in slower nerve fibres resulting in a cAP that have ***multiple peaks*** (figure 31) the number of which also varies according to the types of nerve fibres present in the stimulated nerve.

NEUROMUSCULAR TRANSMISSION

The area of contact between a nerve fibre and a muscle fibre is called the ***motor end plate*** (***M.E.P.***) ***or neuromuscular junction***. As the nerve approaches the muscle, it loses its myelin sheath and its axon is branched. The tip of each branch (= ***sole foot***) is covered by the neurolemma which continues with the sarcolemma (the outer membrane of the muscle fibre). Each sole foot lies in a depression in the plasma membrane (the inner membrane of the muscle fibre) called the ***synaptic gutter,*** where the membrane is thrown into many folds called *the* ***palisades*** (figure 32).

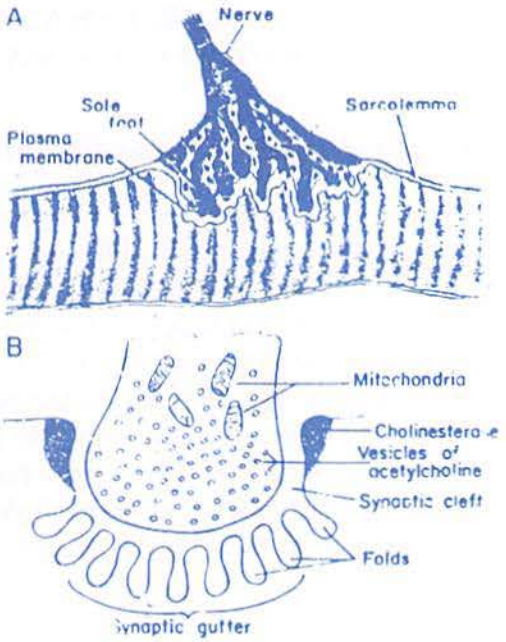


Figure 32 : **(A)** The neuromuscular junction or motor end plate **(B)** The invagination of a sole foot into the plasma membrane of the muscle fibre

There is ***no protoplasmic continuity*** between the nerve and muscle fibres. They are separated by the ***synaptic cleft*** in which the chemical transmitter ***acetylcholine*** is released from the vesicles present in the sole feet. The sarcoplasm at the motor end plate is *granular* and contains the ***cholinesterase enzyme*** (figure 32) which hydrolyzes acetylcholine.

Miniature end plate potential (M.E.P.P.)

This is a state of ***persistent localized subthreshold DP*** (0.5 mV in amplitude) of the muscle fibres at the M.E.P. ***during rest***. It does not reach the firing level (so it does not lead to an AP), and is due to continuous ***release of small amounts of acetylcholine*** (due to continuous rupture of a few vesicles that contain this chemical transmitter at the nerve terminals).

Mechanism of neuromuscular transmission

When a motor nerve is stimulated, the generated impulse is propagated toward the M.E.P., where it causes movement of Ca^{2+} from the extracellular fluid into the nerve terminals. ***Ca^{2+} cause rupture of the acetylcholine vesicles*** leading to release of this transmitter into the synaptic cleft.Acetylcholine then combines with ***nicotinic receptors*** in the muscle membrane and this increases its permeability to Na^+ through opening of ligand-gated Na^+ channels. Accordingly, Na^+ influx increases resulting in DP of the muscle at the M.E.P., which is called the ***end plate potential***. This normally reaches the firing level, which starts an AP along the surface of the muscle. The released acetylcholine is ***rapidly hydrolyzed by the cholinesterase enzyme so that re-excitation of the muscle wouldn't occur*** (page73)

Properties of neuromuscular transmission

(1) At the M.E.P., impulses are ***conducted in one direction only*** (from the nerve to the muscle and not in the opposite direction).

(2) Transmission of impulses at the M.E.P. is ***delayed 0.5 - 0.7 millisecond*** due to the time required for **(a)** Release of acetylcholine **(b)** Passage of acetylcholine across the synaptic cleft and its combination with the nicotinic receptors in the muscle **(c)** Increase in the permeability of the muscle membrane to Na^+ **(d)** Increase in Na^+ influx till the firing level.

(3) Transmission of impulses at the M.E.P. ***readily fatigues*** after repeated stimulations (mostly due to ***exhaustion of acetylcholine***).

(4) Transmission of impulses at the M.E.P.is readily ***affected by drugs*** (see next).

Drugs that affect neuromuscular transmission

(A) Drugs that block neuromuscular transmission

(1) Curare (tubocurarine) and some other related drugs (e.g. ***Flaxedil***), which act by ***competitive inhibition*** (refer to autonomic N.S., page 26).

(2) Botulinum toxin : This toxin inhibits the release of acetylcholine.

(B) Drugs that stimulate neuromuscular transmission

(1) Acetylcholine-like drugs that are not rapidly hydrolyzed by the cholinesterase enzyme and act mainly at the M.E.P. e.g. ***carbachol***.

(2) Drugs that preserve the liberated acetylcholine at the M.E.P. by antagonizing the cholinesterase enzyme e.g. ***prostigmine and eserine*** (refer to the autonomic N.S., page 27).

THE SKELETAL MUSCLE

The human body contains 3 types of muscles, which are the following :

(1) **Skeletal muscles** (= *striated or voluntary muscles*).
(2) **Smooth muscles** (= *plain or involuntary muscles*).
(3) **Cardiac muscle** (= *the muscle of the heart*).

The function of skeletal muscles is ***to move the body and maintain the erect posture***. They are innervated by the axons of the anterior horn cells (A.H.C.) of the spinal cord (figure 33) as well as by the ***motor cranial nerves***. They are under ***voluntary control*** and their activity ***depends completely on their nerve supply***.

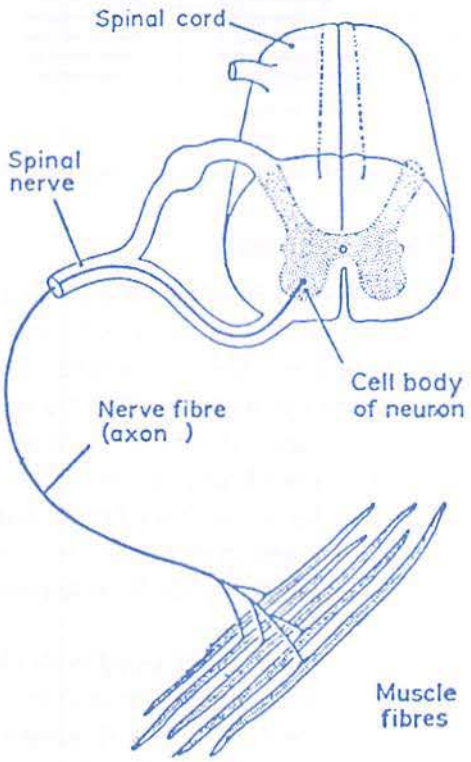


Figure 33 : The motor unit.

The motor neuron pool

This is the ***collection of nerve cells that supply a skeletal muscle***. In the spinal cord, these are the ***anterior horn cells,*** and the cells that supply a certain muscle are usually collected in 1 or more neighbouring segments.

The motor unit

The motor unit (figure 33) consists *of* ***one anterior horn cell + its axon + muscle fibres supplied by this axon*** (which are 3- 6 in the muscles that perform fine movements e.g. muscles of the hand and eye, and 120-165 in

the muscles that perform gross movements e.g. muscles of the leg & back). The threshold for stimulation of different motor units is variable, so. gradually increasing the intensity of stimulation of a nerve trunk or a whole skeletal muscle progressively increases the number of active motor units [indicating that ***nerve trunks and whole skeletal muscles do not obey the all or none law*** (page 31), although each unit by itself obeys this law].

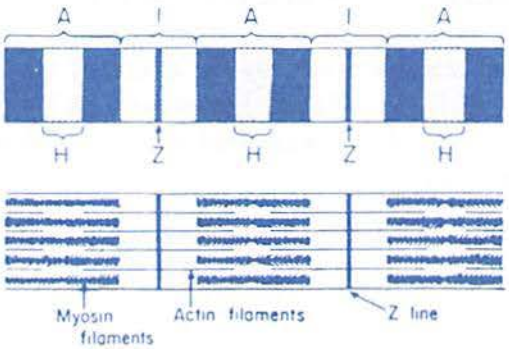


Figure 34 : Histology of the skeletal muscle fibre .

Histology of skeletal muscles

Skeletal muscles are formed of bundles of muscle fibres which are arranged parallel to the longitudinal axis of the muscle and there is ***no connection between adjacent fibres***. Each fibre is a single cylindrical elongated multinucleated cell. It contains cytoplasm called the ***sarcoplasm*** and is surrounded by 2 membranes, the outer of which is called the ***sarcolemma*** and the inner is called the ***plasma membrane*** (figure 32).

In the sarcoplasm, there is a large number *of* ***mitochondria*** as well as large quantities of K^+, Mg^{2+}, PO_4^{3-} and proteins. It also contains ***glycogen*** and other ***energy-producing substances*** specially ***adenosine triphosphate*** (***ATP***) ***and creatine phosphate*** (***CP***).

Each muscle fibre contains hundreds of ***myofibrils*** embedded longitudinally parallel to each other in the sarcoplasm (producing ***longitudinal striations***), and each myofibril consists of several thousand ***filaments*** lying side by side. The latter are made up of the contractile proteins of muscles, which include mainly ***actin and myosin*** as well as 2 other proteins called ***tropomyosin and troponin***. Muscle fibres also show ***cross*** (***transverse***) ***striations*** because the myofibrils contain alternative ***dark (or A) bands*** (= Anisotropic bands) and ***light (or I) bands*** (= Isotropic bands). In the centre of each A band, there is a narrow lighter band called the ***H band*** , and in the centre of each I band there is a dark line called the ***Z line*** (figure 34). The distance between 2 adjacent Z lines is called ***the sarcomere*** (figure 36 a) which constitutes the contractile unit of the muscle fibre.

The myosin molecules are large, and they form ***thick filaments*** that occupy the ***A bands***. On the other hand, the actin molecules are much

smaller, and they form ***thin filaments*** together with both troponin and tropomyosin (figure 36 e) which start at the Z lines and occupy the ***I bands,*** then they extend into the A bands (between the thick filaments) and terminate at the edges of the H bands (figures 34 and 36 a).

In the middle of the H bands there are ***M lines*** which are due to a central bulge in each thick filament (figure 36 a and c).

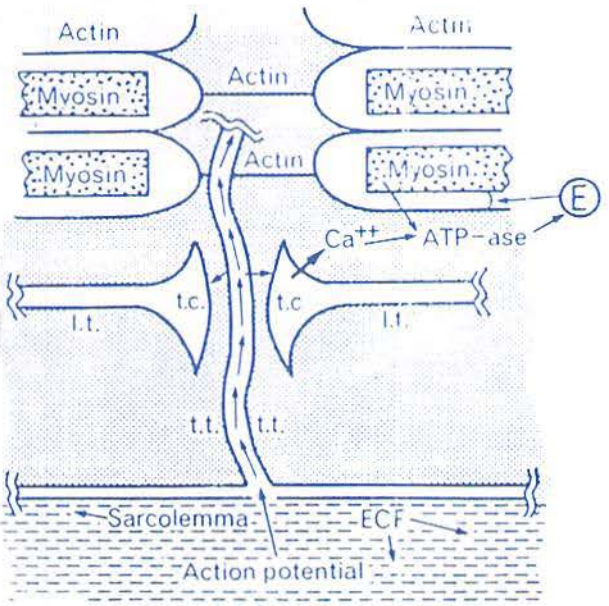


Figure 35 : The sarcotubular system.
t.t. = transverse tubules. l.t. = longitudinal tubules. t.c. = terminal cistern. ECF = Extracellular fluid. E = Energy.

The sarcotubular system

This is a system of tubules located in the sarcoplasm of muscle fibres (figure 35). It is made up of a ***T-system and the sarcoplasmic reticulum.*** The T system consists of **transverse tubules (t.t)** which terminate in the sarcolemma by minute pores ***at the junctions of the A and I bands.*** The walls of the t.t. are continuous with the sarcolemma and they are connected to the extracellular space. The function of the T system is ***rapid transmission of the action potential from the cell membrane to all myofibrils in the muscle fibre.***

The sarcoplasmic reticulum is formed of irregular ***longitudinal tubules*** (lt) that run parallel to and surround the myofibrils. They are dilated at the areas of contact with the t.t. and these dilatations are called ***terminal cisterns.*** The collection of 2 terminal cisterns with the adjacent t.t. is called a ***triad.*** The tubules of the sarcoplasmic reticulum are rich in Ca^{2+} (particularly in the terminal cisterns) which play an essential role in the process of muscle contraction (see below).

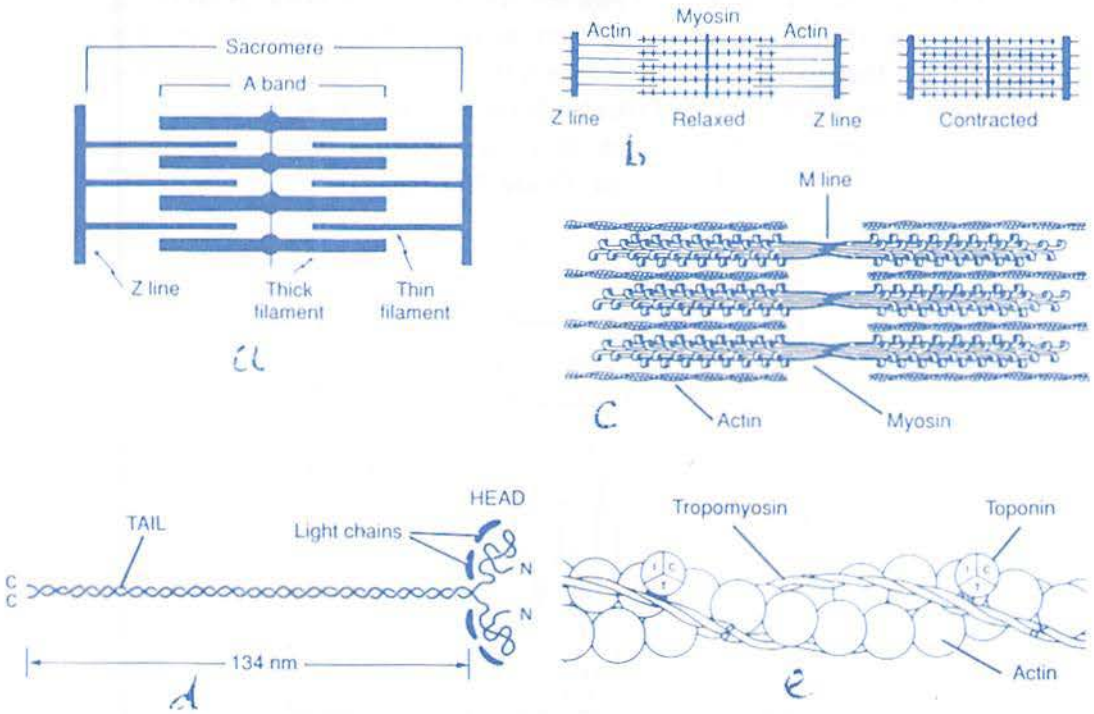


Figure 36 : Arrangement of the skeletal muscle proteins involved in contraction and relaxation **(a)** The contractile unit (= the sarcomere) **(b)** The sarcomere during muscle contraction and relaxation **(c)** Detailed structure of actin (thin) and myosin (thick) filaments **(d)** Structure of the myosin 2 molecule in skeletal muscles **(e)** Arrangement of actin, troponin and tropomyosin in the thin filaments.

Muscle proteins involved in contraction & relaxation

(1) Myosin

This is a complex protein of which there are 2 types :

(a) Myosin 1 : The molecules of this type have a single head and no tail and are present in certain cells in the body but ***not in skeletal muscles***.

(b) Myosin 2 : This is ***present in skeletal muscle fibres***. Its molecules are arranged symmetrically on either side of the centre of the sarcomere (figure 36 c) and each is composed of ***2 heavy and 4 light chains***. The 2 heavy chains wrap spirally around each other (as a double helix) forming a long tail, while their terminal portions combine with the 4 light chains forming ***2 globular heads*** (figure 36 d). These heads contain actin-binding sites and other catalytic sites that hydrolyze ATP. ***Cross bridges*** (***or linkages***) form between the globular myosin heads and the actin molecules, and each cross bridge is flexible at 2 points called ***the hinges***. Such arrangement is important for the processes of muscle contraction and relaxation.

(2) Actin

The actin molecules are ***globular*** in shape and they form the ***thin filaments in the myofibrils together with tropomyosin and troponin*** molecules (see above). Each thin filament contains 300- 400 actin molecules arranged in 2 chains that form a ***long double helix*** (figure 36 e).

(3) Tropomyosin

The tropomyosin molecules are long filaments located in the groove between the 2 chains of actin molecules (figure 36 e), and each thin filament contains 40-60 tropomyosin molecules.

(4) Troponin

The troponin molecules are located at intervals along the tropomyosin molecules (figure 36 e). Like actin, they are ***globular*** in shape and each is made up of 3 subunits that perform specific functions **: (1) Troponin T** binds the other troponin components to tropomyosin **(2) Troponin I** inhibits the interaction between myosin and actin **(3) Troponin C** contains the binding sites for Ca^{2+} that initiate muscle contraction (see below).

MECHANISM OF MUSCLE CONTRACTION

Excitation contraction coupling

This is the *process by which DP of the muscle fibre initiates contraction*. When a nerve impulse arrives at the M.E.P., it leads to release of acetylcholine from the nerve terminals. Acetylcholine then combines with cholinergic nicotinic receptors in the muscle fibre membrane resulting in increased permeability to Na^+. Accordingly, Na^+ influx increases leading to a strong localized DP (= ***end plate potential***). When the latter reaches the firing level (about -40 mV), an AP is produced and is propagated along the muscle membrane ***in both directions*** till the ends of the muscle fibre (the M.E.P. usually lies in the middle of the muscle fibre as shown in figure 33). At the same time, the AP is transmitted ***into the muscle fibre via the transverse tubules*** where it triggers release of Ca^{2+} from the terminal cisterns (figure 37 b) which initiates muscle contraction (see next).

Role of Ca^{2+} in muscle contraction

Muscle contraction occurs as a result of ***sliding of the thin (actin) filaments between the thick (myosin) filaments*** through an interaction between the myosin heads (= ***cross bridges or linkages***) and the actin molecules. In the resting muscle, ***troponin I is tightly bound to actin, and tropomyosin covers the sites where the myosin heads bind to actin***. Thus,

the troponin-tropomyosin complex constitutes a relaxing protein that inhibits the interaction between actin and myosin (figure 38 a).

Ca^{2+} (released by the AP) initiate contraction by binding to ***troponin C***. This weakens the binding of troponin I to actin, which permits tropomyo-sin to move laterally (figure 38 b). Such movement uncovers the binding sites of actin for the myosin heads, starting an interaction between both which leads to sliding of the actin filaments between the myosin filaments resulting in muscle shortening (i.e. contraction). The energy required for this process is provided by breakdown of ATP. The breakdown of ATP to ADP (adenosine diphosphate) is catalyzed by the ***heads of the myosin molecules*** which exert ***an adenosine triphosphatase (ATPase) activity in the presence of*** Ca^{2+} (see below).

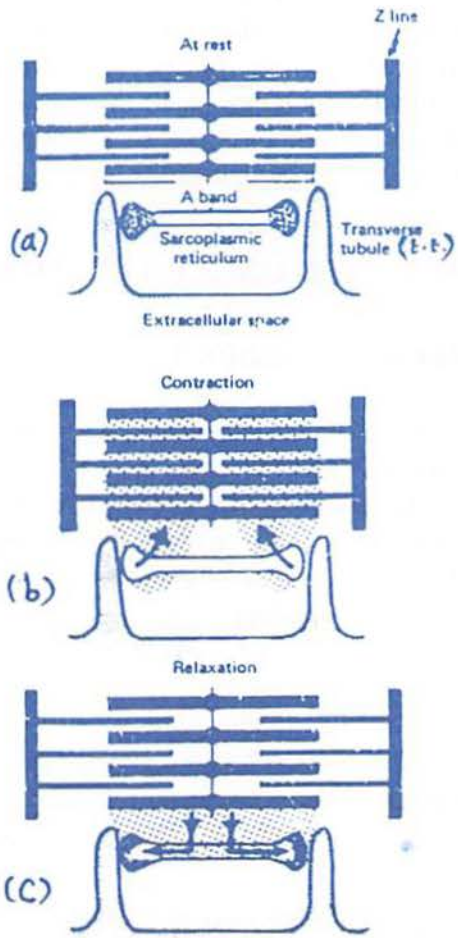


Figure 37 : Muscle contraction and relaxation, **(a)** At rest, Ca^{2+} (the black dots)is stored in the terminal cisterns of the sarcoplasmic reticulum **(b)**The AP spreads via the t.t. and releases Ca^{2+} leading to muscle contraction **(c)** Ca^{2+} is actively pumped into the sarcoplasmic reticulum (and is then stored in the terminal cisterns) leading to muscle relaxation.

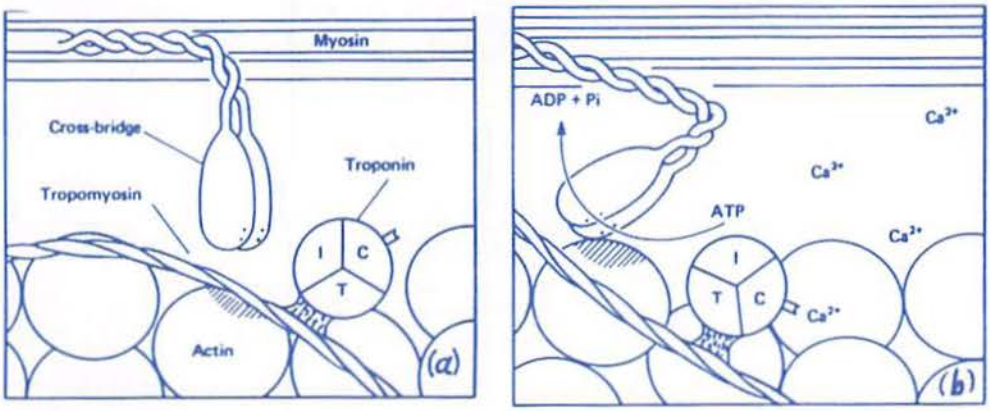


Figure 38 : Initiation of muscle contraction by Ca^{2+} **(a)** At rest, tropomyosin covers the binding sites on the actin molecule (the striped area) **(b)** The myosin heads (cross bridges) attach to the binding sites of actin then tilt when tropomyosin moves laterally by binding of Ca^{2+} to troponin C.

Molecular mechanism of contraction (= sliding or walk along theory)

Muscle shortening during contraction is produced by sliding of the thin filaments between the thick filaments. This sliding is produced by repeated forming then breaking of ***cross linkages between actin and myosin***. The heads of the myosin molecules bind to specific sites at the actin molecules, then they ***tilt at the hinges*** leading to partial sliding of the actin filaments (figure 39). The myosin heads then detach (separate) and re-connect at the next sites of actin, and a new cycle is initiated. This process of binding, tilting and detaching of the myosin heads is repeated, promoting sliding of the actin filaments which leads to muscle shortening.

The attachment of the myosin heads to actin causes a conformational change in these heads and provides the ***power stroke*** for their tilt (which pulls the actin filaments). The energy for this power stroke is supplied by hydrolysis of ATP, and the greater the amount of work performed by the muscle, the more the amount of ATP that is hydrolyzed (= ***Fenn effect***).

Also, each cross bridge operates independently and accordingly, the ***greater the number of cross bridges that contact the actin filaments, the stronger will be the force of contraction***.

Morphological changes after muscle contraction

As the thin filaments slide between the thick filaments, the Z lines move closer and the sarcomeres become smaller. The width of the I bands is decreased, while that of the A bands remains constant (figure 37 b). The ***H bands become narrower*** as the thin filaments from the opposite ends of the sarcomeres approach each other, and when muscle shortening is marked, these filaments overlap and the H bands disappear (figure 36 b).

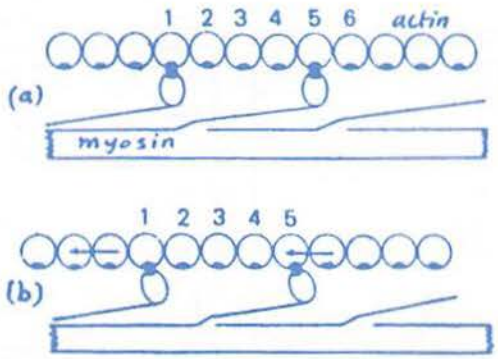


Figure 39 : The sliding mechanism of muscle contraction **(a)** Binding of the myosin heads (cross bridges) to active sites at the actin molecules **(b)** Tilting of the myosin heads leading to partial sliding of the actin filament.

Mechanism of muscle relaxation

Shortly after Ca^{2+} ions are released from the terminal cisterns of the sarcoplasmic reticulum (which initiates the contraction process), they are ***actively re-uptaken back into the longitudinal tubules of the sarcoplasmic reticulum by an active Ca^{2+} pump***. Ca^{2+} ions then diffuse to the terminal cisterns where they are stored (figure 37 c).

Once the Ca^{2+} concentration outside the sarcoplasmic reticulum is lowered, the troponin-rtropomyosin complex regains its original position, leading to separation of the myosin heads (cross bridges) from actin. Thus the interaction between myosin and actin stops and, accordingly, the actin filaments slide back to the resting position resulting in muscle relaxation.

The energy for the active Ca^{2+} pump is provided by breakdown of ATP (therefore, **both contraction and relaxation of the muscle require ATP**). Accordingly, if ATP is depleted, the muscle does not relax leading to a state of sustained contraction called **contracture** (page 75).

CHANGES THAT ACCOMPANY MUSCLE CONTRACTION

(1) ELECTRIC CHANGES

These (as well as the accompanying ionic changes) are similar to those occurring in nerves with slight differences, which include the following :

(1) The resting membrane potential in muscles is about *-90* mV(while it is about -70 mV in nerves).

(2) An effective stimulus causes a local response and the firing level is reached at about -40 mV (while it is about -55 mV in nerves).

(3) The stimulus causes DP followed by reversal of polarity (overshoot) which reaches up to +40 mV (while it reaches +35 mV in nerves).

(4) The magnitude of the spike in muscles is about 130 mV (from -90 to +40 mV), while it is about 105 mV in nerves (from -70 to +35 mV).

(5) The duration of the spike is longer in muscles (2- 4 msec), while it is only 2 msec in nerves.

(6) The spike is propagated along the surface of the muscle at a rate of about *5 meters / second* while it is variable in nerves depending on their diameters (page 47).

(7) In both muscles and nerves, the spike is followed by after-depolarization then by after-hyperpolarization, but their durations are relatively longer in muscles.

(8) The ***chronaxie is generally longer in skeletal muscles*** than in nerves (indicating that the muscles are less excitable than nerves).

(2) EXCITABILITY CHANGES

These are also similar to those occurring in nerves when stimulated. Thus, during activity, skeletal muscles pass in **4 phases of excitablilitv** i.e. absolute refractory period ***(ARP)***, relative refractory period (***RRP***) , a ***supernormal phase*** and a ***subnormal phase*** (refer to the excitability changes in nerves, page 44).

(3) METABOLIC (CHEMICAL) CHANGES

Chemical composition of skeletal muscles

Skeletal muscles constitute approximately ***40 % of the total body weight*** and they consist of the following substances :

1. **Water :** About 75- 80 %.
2. **Proteins** (actin, myosin, troponin, tropomyosin) **:** About 20 %.
3. **Energy-producing substances :** Adenosine triphosphate (**ATP**) and phosphorylcreatine (= creatine phosphate or **CP**) as well as glycogen.
4. **Inorganic ions :** Cations include K^+ , Mg^{2+} and Ca^{2+}, while anions include HCO_3^- , Cl^- , SO_4^{2-} and PO_4^{3-}.

The osmolality of the sarcoplasm is isotonic (i.e. equal) to that of the plasma i.e. equivalent to ***0.9 % NaCl solution*** (refer to blood).

Metabolism during rest

During rest, skeletal muscles consume about 60 ml O_2 / minute for production of energy, which is used for the following :

1. Maintenance of the resting membrane potential (Na^+ - K^+ pump).
2. Chemical synthesis of various substances e.g. proteins and glycogen.
3. Production of muscle tone (= continuous partial muscular contraction during rest) which is discussed in detail in the C.N.S.

Metabolism during muscular contraction

Skeletal muscles act as ***machines that convert chemical energy into mechanical energy***. During contraction, the metabolic rate of muscles markedly increases and excess energy is produced. This takes place through a series of **anaerobic reactions** which occur as follows :

(1) The first step is breakdown of ATP to ADP (adenosine diphosphate). This releases a great amount of energy which is delivered to the contractile proteins as shown in the following reaction :

$$ATP + H_2O \xrightarrow{\text{ATP-ase}} ADP + H_3PO_4 + \text{Energy (7.3 KCal)}$$

(2) The second step is rapid regeneration of ATP from ADP. This reaction is ***endothermic*** i.e. needs energy, which is obtained from the breakdown of CP as shown in the following reaction :

$$ADP + CP \xrightarrow{\text{creatine phosphokinase}} ATP + \text{Creatine}$$

(3) The third step is a slower regeneration of both ATP and CP from glucose (or glycogen) breakdown. Glucose is derived from both the blood stream and muscle glycogen. In the muscles, glucose is degraded to pyruvic acid, the fate of which depends on the O_2 supply as follows :

(a) If O_2 supply is adequate, pyruvic acid enters the citric acid cycle and; is metabolized to CO_2 and H_2O. This process is called **aerobic glycolysis,** and is associated with liberation of a great amount of energy sufficient to form large quantities of ATP as shown in the following reaction :

$$\text{Glucose} + 2\ ATP \xrightarrow{\text{oxygen}} 6\ CO_2 + 6\ H_2O + 40\ ATP$$

(b) If O_2 supply is insufficient, pyruvic acid is reduced to lactic acid. This process is called **anaerobic glycolysis,** and is associated with liberation of a much smaller amount of energy that results in formation of a small quantity of ATP as shown in the following reaction :

$$\text{Glucose} + 2\ ATP \xrightarrow{\text{anaerobic}} 2\ \text{lactic acid} + 4\ ATP$$

Anaerobic glycolysis is **self-limiting** and lasts for only a short time because the accumulated lactic acid eventually exceeds the capacity of the tissue buffers leading to a decline in pH (which inhibits the enzymatic reactions involved in muscle contraction, resulting in fatigue). However, it is greatly useful since it permits muscular activity in the start of a muscular exercise when the O_2 supply is still inadequate.

Fate of lactic acid

(1) Oxidation during the recovery period (which follows muscular activity) ***to pyruvic acid,*** which is further oxidized in the Kreb's (= citric acid) cycle producing energy that is used for resynthesis of ATP and CP. The extra amount of O_2 used during the recovery period for lactic acid oxidation is called the **O_2 debt** (refer to energy metabolism book).

(2) Diffusion to the bloodstream, then to the liver where it is converted to glycogen.

(3) It is the best ***fuel to the heart*** (i.e. it is oxidized in the cardiac muscle, producing the necessary energy for its contraction).

Free fatty acids (FFA) can also be oxidized in skeletal muscles to produce energy. FFA are probably the ***main substrates that supply energy for skeletal muscles at rest and during the recovery period following contraction*** for resynthesis of ATP as shown in the following reaction :

$$\text{FFA} \xrightarrow{\text{oxygen}} CO_2 + H_2O + \text{ATP}$$

pH changes in skeletal muscles during contraction

During contraction, the pH in skeletal muscles changes as follows :

(1) It initially becomes ***acidic*** (due to H_3PO_4 formed as a result of ATP breakdown).

(2) It then becomes slightly ***alkaline*** (due to creatine formed as a result of CP breakdown).

(3) It becomes ***acidic*** again (due to lactic acid formed as a result of glucose breakdown).

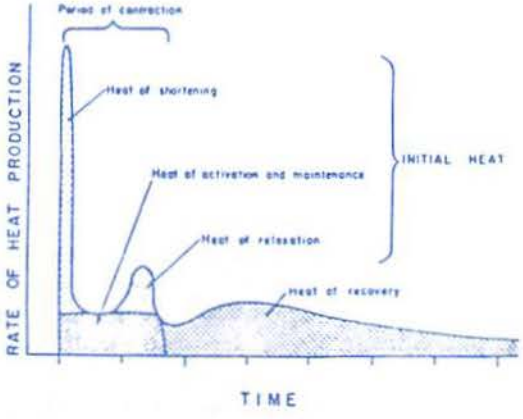


Figure 40 : Heat production in skeletal muscles during & after contraction

(4) THERMAL CHANGES

The heat produced by skeletal muscles during rest is called the resting heat and is the external manifestation of the basal metabolic processes in the muscles. During contraction, the heat production in skeletal muscles is markedly increased, and is liberated in 2 phases (figure 40) :

(A) INITIAL HEAT

This heat is liberated during muscular activity, and it includes :

(1) Activation and maintenance heat : This is liberated as a result of the chemical processes that initiate and maintain muscular contraction.

(2) Shortening heat : This is liberated if the muscle shortens,therefore it occurs only during ***isotonic contractions*** (see below), and it represents an increased rate of energy liberation by the cross bridges as the actin filaments slide over the myosin filaments.

(3) Relaxation heat : This is an extra heat that is liberated during muscular relaxation, and its exact source is not settled. However, work should be done to return the muscle to its previous length, and the relaxation heat is believed to be a manifestation of this work.

(B) RECOVERY (DELAYED) HEAT

This heat is liberated ***after stoppage of contraction***. It is produced as a result of the ***chemical processes that restore the chemical composition of the muscles to its pre-contraction state***. It is approximately ***equal to the initial heat,*** and it continues for as long as 30 minutes after muscle contraction stops. Most of this heat results from oxidation of ***free fatty acids and lactic acid*** to supply the energy required for resynthesis of ATP

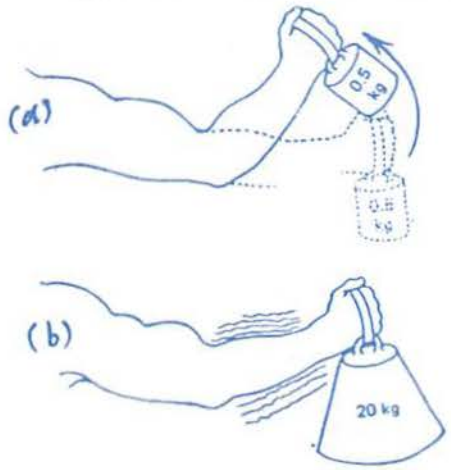


Figure 41 : Types of muscle contraction **(a)** Isotonic contraction (the biceps muscle shortens and the weight is lifted) **(b)** Isometric contraction (the biceps muscle does not shorten and the weight is not lifted).

(5) MECHANICAL CHANGES

TYPES OF MUSCLE CONTRACTION

(1) ISOTONIC CONTRACTION

This occurs when lifting loads having moderate weights (figure 41 a). The muscle ***shortens and becomes thicker*** (but the *muscle tension remains constant*), and the ***load is moved,*** thus an ***external work is performed*** [*which equals weight (in Kg)* x *distance it is moved (in meters)*].

(2) ISOMETRIC CONTRACTION

This occurs when lifting too heavy loads to be moved (figure 41 b). The muscle ***does not shorten*** (but the ***muscle tension is markedly increased***). and the ***load is not moved***. Therefore, ***no external work is performed***. Maintenance of the ***erect posture against the force of gravity*** is also a type of isometric contraction.

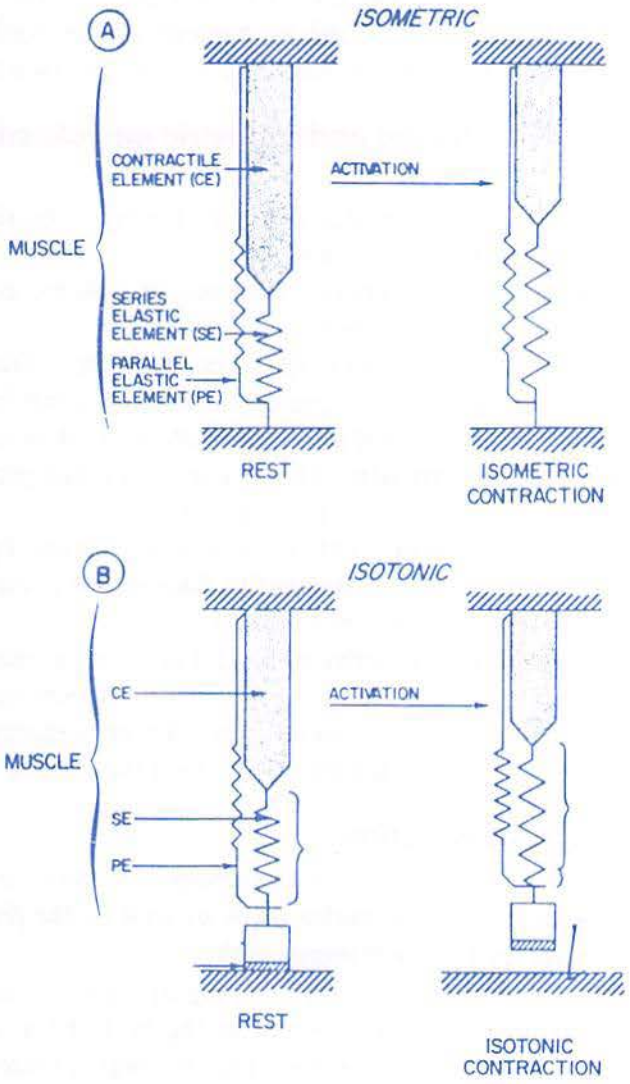


Figure 42 : Series elastic element (**SE**) and contractile element (**CE**) during an isometric contraction **(a)** and an isotonic contraction **(b)**.

** In addition to the ***contractile element*** (CE) in skeletal muscles (i.e. the muscle fibres), there are also ***2 elastic elements*** (figure 42) **:** one parallel to the CE and the other in series with it. *The **parallel***

element **(PE)** is present in the connective tissue sheaths that lie parallel to the muscle fibres, while the ***series elastic element*** **(SE)** is present mainly in the tendons. The ***element that mainly stretches during contraction is the SE***. In isometric contractions, the CE shortens and the SE is greatly stretched (because the load is not moved) and accordingly, the whole muscle is not shortened and its tension markedly increases. On the other hand, in isotonic contractions, the CE also shortens but the SE is not markedly stretched (because the load is moved) and accordingly, the whole muscle is shortened and its tension remains constant (see above).

Differences between isotonic and isometric muscle contraction

(1) Muscle length : This is decreased in isotonic contractions but remains constant in isometric contractions.

(2) Muscle tension : This remains constant in isotonic contractions but is increased in isometric contractions.

(3) Energy of contraction : In isotonic contractions, this energy is converted partly to external work and partly to waste heat, but in ***isometric contractions all energy is converted to waste heat*** (no work is performed).

(4) Sliding of actin into myosin : This occurs to a much greater extent in isotonic contractions (since work is performed).

(5) Duration of contraction : This is longer in isotonic contractions because a load is moved (which prolongs the duration of contraction due to the inertia and momentum of the movement).

(6) Oxygen and nutrient requirements : These are greater in isotonic contractions because more energy is needed for work performance.

(7) Heat production : This is usually greater in isometric contractions because all energy is converted into waste heat (see above).

Strength of muscle contraction

The strength of muscle contraction (whether isotonic or isometric) depends on the ***number of active motor units as well as ike frequency of nerve impulses discharged in each motor unit***.

Human skeletal muscles can exert 3- 4 Kg of tension / cm^2 of cross-sectional area. Since many of the muscles in the body have a relatively large cross-sectional area, the tension they can develop is quite large (e.g. the gluteus maximus muscle can exert a tension of 1200 Kg). The total tension developed by all muscles in an adult man is about ***22000 Kg***.

MUSCLE TENSION

Passive tension is that exerted by the unstimulated muscle while ***total tension*** is that which the muscle develops when stimulated to contract ***isometrically***. The difference between both is called ***active tension*** (which is the amount of tension actually generated by the contractile process).

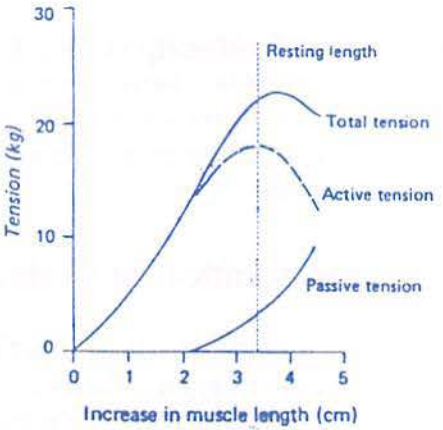


Figure 43 : Length-tension relationship for the human triceps muscle.

Length-tension relationship in skeletal muscles

As the muscle is stretched (i.e. lengthened), passive tension rises slowly at first then more rapidly (figure 43)., and it ***ruptures when stretched to about 3 times its equilibrium length*** (= length of the relaxed muscle cut free from its bony attachments). On the other hand, the active and total tensions rise to a maximum then decline. It was found that the length of most muscles in the body at rest (= **resting length**) is the length at which they develop maximal active tension.

The relation between length and tension is explained by the ***sliding mechanism***. When the muscle contracts *isometrically*, the developed tension is proportionate to the number of cross-linkages between actin and myosin. If the muscle is excessively stretched, the overlap between actin and myosin is reduced, so the number of cross-linkages and the muscle tension are decreased. Similarly, if the muscle is shorter than the resting length, the actin filaments overlap and this also causes reduction of the number of the cross-linkages and decreases the developed tension.

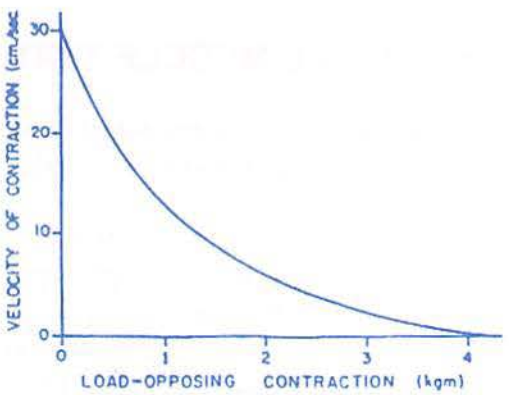


Figure 44 : Effect of load on the velocity of muscle contraction.

Relation between load and velocity of contraction

The velocity of muscle contraction ***varies inversely with the load*** on the muscle (figure 44). As in case of muscle tension, the velocity of contraction at a given load is maximal at the resting length, and it decreases if this length is increased or decreased.

Effect of a single stimulation of skeletal muscles

Skeletal muscles can be stimulated either ***directly or indirectly*** (the latter ***through stimulating its nerve supply***). According to the strength of the stimulus, one of the following effects may be obtained :

(1) A subthreshold (= subminimal) stimulus produces no contraction.

(2) A threshold (minimal) stimulus leads to contraction of the most excitable muscle fibres (producing a weak contraction).

(3) A supraminimal stimulus leads to contraction of a greater number of muscle fibres (producing a stronger contraction).

(4) A maximal stimulus leads to contraction of all muscle fibres (producing a maximal contraction).

(5) A supramaximal stimulus leads to the same effect as the maximal stimulus because ***each muscle fibre obeys the all or none law.***

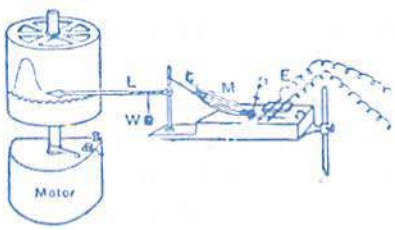


Figure 45 : A nerve-muscle preparation for recording isotonic contractions. **n** = Sciatic nerve. **m** = Gastrocnemius muscle. **l** = Lever, **w** = Weight. **t** = Thread. **e** = Stimulating electrodes. **p** = Pin at the knee joint.

THE SIMPLE MUSCLE TWITCH

This is a ***brief (short) muscle contraction followed by relaxation***. It is produced by ***a single maximal stimulus***, and either an isotonic or isometric contraction can be recorded.

(1) The isotonic twitch is obtained by stimulating the muscle ***indirectly*** (i.e. through its nerve supply) using a simple apparatus (refer to the practical book). The frog's gastrocnemius muscle is dissected with its nerve supply (the sciatic nerve), and is fixed at the knee joint with a pin (figure 45). Its tendon is tied to a thread which is attached to a lever, and a pointer is fixed to the lever which records the contraction on a moving

drum. The nerve is stimulated by 2 electrodes connected to an electronic stimulator, and the record obtained shows ***changes in the length*** of the stimulated muscle.

(2) The isometric twitch is obtained by an apparatus shown in figure 46, in which the muscle is stimulated ***directly***, and it shows ***changes in the tension*** of the stimulated muscle. An isolated muscle is attached between 2 fixed points (***a solid rod and a powerful spring of a force transducer***). Such arrangement prevents muscle shortening, and the developed muscle tension pulls on the spring of the transducer. The latter transforms the mechanical energy into electric activity that can be amplified and recorded (e.g.. by a cathode ray oscilloscope).

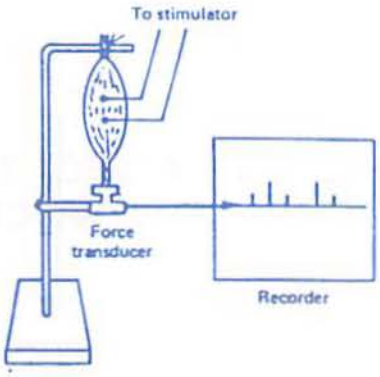


Figure 46 : Method of recording isometric muscle contractions.

Both the isotonic and isometric twitches consist of the following 3 phases :

(1) Latent period : In case of isotonic twitches (figure 47) the latent period is the time between the application of the stimulus and start of the contraction, and it is normally about ***0.01 second***. It represents the time needed for **(a)** conduction of the nerve impulse along the nerve fibre **(b)** development of the end plate potential **(c)** conduction of the impulse along the surface of the muscle **(d)** development of the mechanical response **(e)** conduction of the response to the recording drum.

(2) Contraction period : During this period, the muscle shortens and performs work in isotonic contractions (or its tension increases in isometric contractions). It lasts about ***0.04 second in isotonic contractions***.

(3) Relaxation period : During this period, the initial length of the muscle is restored in isotonic contractions (or the muscle tension drops to the resting level in isometric contractions). It lasts about ***0.05 second in isotonic contractions***.

Therefore, the whole isotonic twitch of ***frog's muscle lasts about 0.1 second***. In mammalian muscles, it is shorter (about 0.08 second). The duration of various phases in ***an isotonic twitch*** can be determined by

recording the vibrations of a tuning fork that has a frequency of 100 vibrations / second, so each vibration plotted on the curve equals 0.01 second (lower record in figure 47).

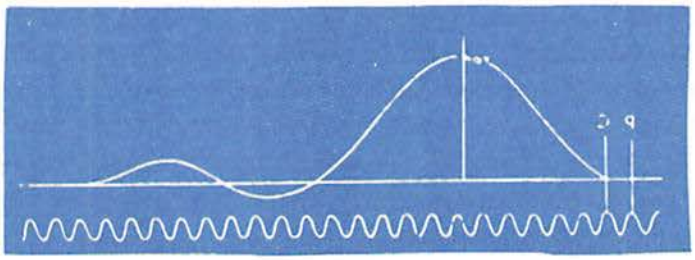


Figure 47 : A simple muscle twitch (isotonic contraction). P = point of stimulation. C = start of contraction. P-C interval = latent period.

FACTORS THAT AFFECT THE SIMPLE MUSCLE TWITCH

(1) TYPE OF MUSCLE

Human skeletal muscles contain ***2 types of muscle fibres*** :

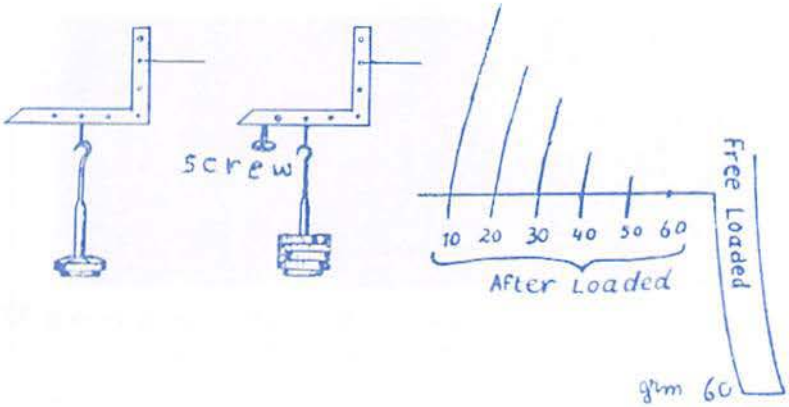
(a) Red muscle fibres : These are also called ***type I fibres*** (or slow oxidative fibres), and they have moderate diameters. They are dark red in colour because they are rich in the red pigment called ***myoglobin***. Muscles rich in these fibres are called ***red or slow muscles***. They have a relatively long latent period and they ***respond slowly*** (i.e. they contract and relax slowly), so they are ***not easily fatigued***. They are ***specialized for gross sustained movements*** and, accordingly, they are adapted for the ***long, slow posture-maintaining contractions*** (e.g. the long muscles of the back).

(b) White (or pale) muscle fibres : These are also called *type* ***II B fibres*** (or fast glycolytic fibres), and they have ***large diameters***. Muscles rich in these fibres are called ***white or fast muscles*** (or pale muscles because their colour is pale red). They have a short latent period and ***they respond rapidly*** (i.e. they contract and relax rapidly), so they are ***easily fatigued.*** They are specialized for ***fine skilled*** (= ***precise***) ***movements*** (e.g. the extraocular muscles and some hand muscles).

** There is another type of skeletal muscle fibres called ***type II A fibres*** (= fast oxidative red fibres) but these fibres are ***rare in human beings***.

(2) INITIAL LENGTH OF THE MUSCLE

The strength of muscle contraction in isotonic contractions (or the developed tension in isometric contractions) is directly proportional within liriiits to the initial length of the muscle (figure 43). This is known as ***Starling's law*** (which also applies to the cardiac and smooth muscles).



Fignre 48 : Free and after-loaded muscle contraction.

In the laboratory, isolated muscles become shorter than their lengths in the body (due to their *elastic components*). In this case, up to a certain limit, as a muscle is stretched its initial length increases and its contraction (or developed tension) also increases, but if the muscle is overstretched, the muscle response becomes weaker.

Inside the body, the ***resting length of most muscles is the length that gives maximal strength of contraction*** (or maximal tension in case of isometric contractions), and either an increase or a decrease in this length would reduce the force of contraction (figure 43).

The effect of the initial length of muscles on the strength of contraction can be demonstrated by the ***free and after-loaded muscle contraction experiment*** (figure 48). In case of **a free-loaded contraction**, a weight is attached to the tendon (or lever) and is allowed to pull freely on the muscle while it is relaxed, so increasing its initial length and affecting it before contraction starts. In case of **an after-loaded contraction**, the weight is also attached to the tendon (or lever), but it is supported during relaxation (by a screw), so it ***does not pull on the muscle during rest***, but it will affect it after contraction starts.

The apparatus is prepared first to record after-loaded contractions, and the weights are gradually increased. It will be noted that as the weights are increased, the strength of the successive contractions is gradually decreased till no contraction is obtained (figure 48). Now, *removal of the support* (which makes the load to be free and stretches the muscle) then stimulating the muscle leads to a strong contraction which lifts the free-loaded weight (figure 48). This is because the initial length of the muscle has increased after removal of the support (as a result of pulling of the free weight on the muscle).

(3) TEMPERATURE

Warming skeletal muscles leads to faster and stronger contractions than

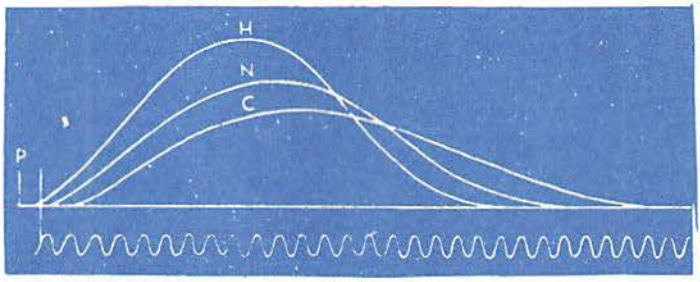


Figure 49 : Effect of temperature on the simple muscle twitch. N = normal. H = hot (or warm). C = cold.

normal (so the amplitude of a muscle twitch is increased together with shortening of its phases).On the other hand, cooling these muscles produces opposite effects (figure 49). The effects of warming are due to ***acceleration of the chemical reactions in the muscle and reduction of its viscosity*** (which facilitates the process of contraction). Conversely, cooling ***slows the chemical reactions and increases the muscle viscosity*** (leading to a weak contraction and prolongation of all phases of the twitch).

** Heating a skeletal muscle above 45 °C leads to its stiffening due to coagulation or denaturation of its proteins (= ***heat rigor***, page 76).

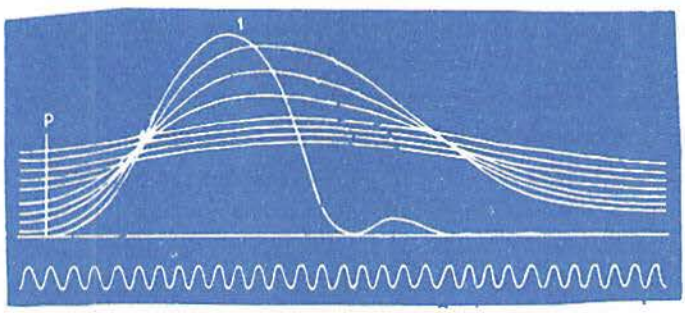


Figure 50 : Effect of fatigue on the simple muscle twitch. 1 = contraction at rest. The lower 3 curves = contracture.

(4) FATIGUE

Repeated ***indirect*** stimulation of a skeletal muscle (through its motor nerve supply) ***decreases the strength of its contraction and prolongs all phases of the simple muscle twitch*** (figure 50) specially the relaxation phase (like cold). After fatigue has occurred, if the stimulating electrodes are transferred to the muscle (to stimulate it directly), it will respond. This means that ***fatigue has not occur in the muscle itself*** but in either the nerve or the motor end plate (M.E.P). Since ***the nerve*** **is** ***not readily fatigued*** (see below), fatigue must have ***occurred in the M.E.P. mostly due to exhaustion of the chemical transmitter*** (***acetylcholine***) as a result of repeated stimulation of the nerve (page 49). Subsequent repeated

stimulation of the muscle itself will also lead to fatigue ***mostly due to reduction of the sources of energy*** (particularly ATP), and muscle relaxation becomes incomplete leading to ***contracture*** (page 75)

Experimental evidence that nerves do not fatigue

In a nerve-muscle preparation (figure 45), ***a segment of the nerve between the stimulating electrodes and the M.E.P. is blocked*** (e.g. by cocaine) and the nerve is stimulated for several hours. ***The block is then removed and the nerve is stimulated.*** It will be found that ***muscle contraction still occurs***, indicating that the nerve has not get fatigued

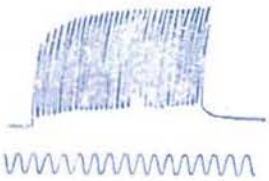


Figure 51 : Staircase (treppe) phenomenon. Note the initial gradual increase in the amplitude (height) of contraction.

Staircase (= treppe) phenomenon

This phenomenon is observed in both ***skeletal and cardiac muscles***. If a series of ***maximal stimuli*** is successively applied to these muscles, the first few contractions gradually increase in strength then the muscle strength becomes constant (figure 51). The gradual rise in the amplitude of the successive twitches is ***similar to the steps of a stair*** (hence the name).

The cause of this phenomenon was believed to be only due to ***warming up of the muscle*** by the successive contractions (i.e. the heat liberated as a result of a contraction leads to warming of the muscle which increases the strength of the subsequent contraction). However, the main cause was found to be ***an increased availability of*** Ca^{2+} inside the muscle fibres (as a result of successive stimulations) which leads to more binding of Ca^{2+} to troponin C, thus producing stronger contractions.

** The gradual increase in the strength of successive contractions is **not against the all or none law** because this law is valid only when all factors that affect muscle contraction remain constant. In this condition, however, as a result of successive stimulations of the muscle, the intramuscular conditions are changed (whether warming or increased Ca^{2+} content) which lead to these progressively stronger contractions.

Relation between electric and mechanical responses

This relation is shown in figure 52, in which the electric changes i.e. the action potential (AP) and the mechanical response are simultaneously recorded. From the tracing, the following points are to be noted :

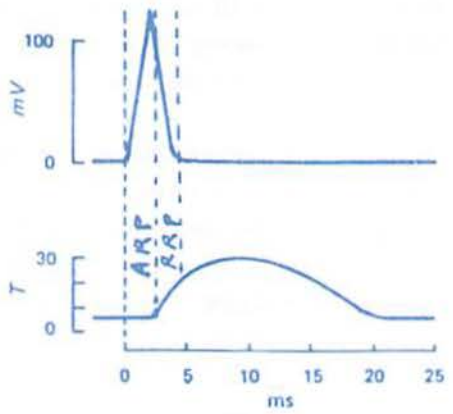


Figure 52 : A simultaneous record of the electric and mechanical responses of a skeletal muscle fibre to a maximal stimulus. (T = tension).

(1) The mechanical response starts about 2 milliseconds after the start of the AP and this period is the ***latent period of the twitch*** (page 66). This period coincides with the ascending limb and upper part of the descending limb 6f the AP i.e. with the **ARP** (page 44). ***Therefore, during the latent period, the muscle is completely inexcitable***.

(2) The initial half of the contraction phase coincides with the remaining part of the descending limb of the AP i.e. with the **RRP** (page 44). Therefore, ***during the contraction phase, skeletal muscles can effectively respond to another stimulation*** (see next).

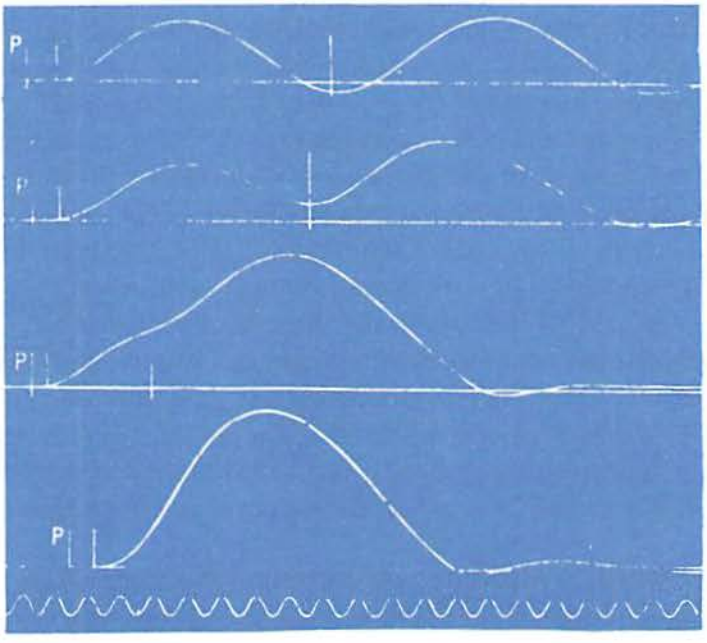


Figure 53 : The effect of 2 successive stimuli (P = point of stimulation).

SUMMATION OF CONTRACTIONS

Since the contraction phase in skeletal muscles starts after the end of the ARP (figure 52), stimulation of these muscles during both the contraction and relaxation phases of a twitch leads to an increasing response. This effect is known as ***summation of contractions***, and it can experimentally be demonstrated by studying the effects of successive stimulation of the muscle. This includes the following 2 experiments :

(A) The effect of 2 successive stimuli

The response of a skeletal muscle to 2 successive stimuli ***depends on the time interval between both***. Accordingly, one of the following responses may be obtained (figure 53) :

(a) If the second stimulus falls ***in the latent period*** (i.e. at the ARP) of the first twitch, it will be ***ineffective*** i.e. it produces no response (figure 53 a).

(b) If the second stimulus falls ***during the contraction phase*** (i.e.at the RRP) of the first twitch, the muscle responds by ***a new contraction*** that is summated to the preceding one resulting in a stronger and more prolonged contraction (figure 53 b).

(c) If the second stimulus falls ***during the relaxation phase*** of the first twitch, ***a curve with 2 peaks*** (***or 2 humps***) ***is produced*** (figure 53 c).

(d) If the second stimulus falls ***soon after the relaxation phase*** of the first twitch, ***2 separate twitches are produced***, the second of which being slightly higher in amplitude (figure 53 d) due to the *staircase phenomenon*.

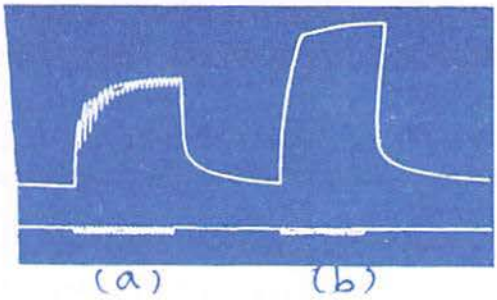


Figure 54 :Genesis of tetanus (a) Incomplete tetanus (b) Complete tetanus.

(B) The effect of repeated stimulation (genesis of tetanus)

The response of a skeletal muscle to multiple successive stimuli ***depends on the frequency (or rate) of stimulation*** as follows :

(a) If the frequency of stimulation is low, so that the stimuli fall ***soon after the relaxation phases*** of the preceding twitches, ***separate twitches*** that show the ***staircase phenomenon*** are produced (figure 51).

(b) If the frequency of stimulation is increased so that the stimuli fall ***during the relaxation phases*** of the preceding twitches, ***incomplete tetanus*** (=***clonus***) is produced, which consists of successive tremulous contractions. From the record, the *number of stimuli which produces this*

effect can be calculated. It is equal to the number of contractions present on the summit of the mechanical response (figure 54 a).

(c) If the frequency of stimulation is further increased so that the stimuli ***fall at the contraction phases*** of the preceding twitches, ***complete tetanus*** (i.e. continuous contraction) is produced (figure 54 b). The number of stimuli that produces complete tetanus ***cannot be predicted from the mechanical response because the successive contractions fuse with each other producing a continuous contraction*** (figure 54 b). However, their number ***can be calculated from the recorded action potentials*** because there is ***no fusion between the action potentials*** (figure 55).

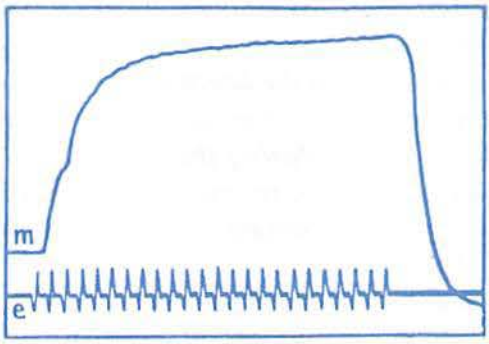


Figure 55 : Mechanical response (m) and electric response i.e. AP (e) in complete tetanus. *Note fusion of (m) but not (e)..*

Factors that affect the number (or frequency) of stimuli required to produce complete tetanus

(1) Nature of muscle : Red muscles (which have long contraction phases) require ***a lower number of stimuli to develop complete tetanus***, compared with white muscles.

(2) Cooling and fatigue : These factors prolong the contraction phase, so they ***lower the number of stimuli required to produce complete tetanus***.

(3) Anticholinesterase drugs (*e.g. prostigmine*) **:** These drugs ***lower the number of stimuli required to produce complete tetanus*** because they preserve acetylcholine at the M.E.P., leading to repeated excitations for each single stimulation of the nerve (*normally, a single stimulus produces only one excitation in the M.E.P. and no more, page 49*), thus a ***smaller number of nerve impulses*** will be enough to produce complete tetanus.

Effect of temperature on tetanus

Cold application converts incomplete tetanus to complete tetanus (figure 56) *without changing the frequency of stimuli*. This is because cold prolongs all phases of the twitch (including the contraction phase), so ***the stimuli which were falling during the relaxation phases*** (*producing*

incomplete tetanus*) *will fall in the contraction phases by effect of cold resulting in complete tetanus (the diagram in the square in figure 56).

On the other hand, ***hot application converts complete tetanus to incomplete tetanus*** *without changing the frequency of stimuli* because heat shortens all phases of the twitch, so ***the stimuli which were falling in the contraction phases*** (***producing complete tetanus***) ***will fall in the relaxation phases by effect of heat*** resulting in incomplete tetanus.

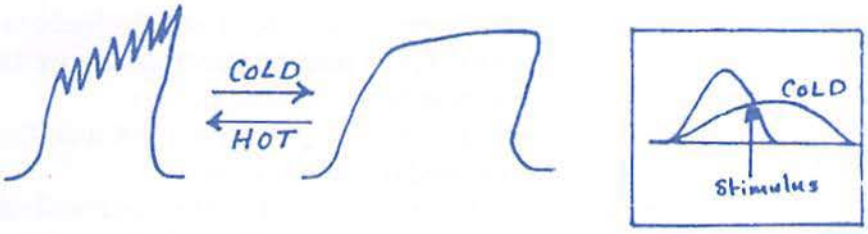


Figure 56 : Effect of temperature on tetanus

MUSCLE TRAINING

Sustained (i.e. continuous) muscular activity (as in athletes) produces hypertrophy of skeletal muscles, together with the following changes in :

(1) Structure : The sarcolemma becomes tough and the amount of connective tissue increases (*so hard-working animals have tough meat*). The muscle fibres increase in thickness (but not in number) and gain an increase in the number of myofibrils.

(2) Strength : The strength of the muscle is increased by training. Up to a certain limit, this is ***directly proportional to the cross section*** **of** the muscle (so the greater the hypertrophy the more will be the strength of the muscle). ***Idle fibres*** (= ***inactive fibres***) ***are also brought into action.***

(3) Endurance : This is increased because the energy-producing substances in the muscles (***ATP, CP and glycogen***) become more available and are stored in greater amounts, and also due to *increased capillarization* of the muscle (which leads to more O_2 supply).

(4) Speed : The speed of muscule contraction increases by training because the ***neuromuscular transmission at the M.E.P. is facilitated.***

MUSCLE FATIGUE

This is a temporary decrease in the work capacity of skeletal muscles following prolonged or forceful contraction. It is mainly due to ***reduction of the energy-producing substances*** (ATP, CP and glycogen) and accumulation of lactic acid , particularly if the blood or O_2 supply was deficient. ***Fatigue in the synapses of the C.N.S. is also a factor*** in production of muscle fatigue after prolonged activity.

MUSCLE CONTRACTURE

This is a state of sustained muscle contraction that is ***not initiated by an action potential***, and it often occurs when the muscles are over-worked or fatigued (page 70). It is due to ***depletion of ATP***, thus the energy required for active Ca^{2+} re-uptake by the sarcoplasmic reticulum after contraction is decreased. Consequently, muscle relaxation fails and the combination between actin and myosin persists leading to contracture (page 57).

EFFECTS OF MUSCLE DENERVATION

Injury to the motor nerve that supplies a skeletal muscle leads to its ***flaccid paralysis***, a condition called ***lower motor neuron lesion*** (refer to C.N.S.). In addition, the following manifestations also occur :

(1) Muscle atrophy (= decrease in size), and within 2-4 months the muscle fibres will be gradually replaced by fibrous tissue.

(2) Muscle fibrillations : These are fine irregular contractions of individual muscle fibres which are ***invisible by the naked eye***, but the electric activity they produce can be recorded by electromyography (see below). They are a sign of ***muscle degeneration*** (so they disappear if the motor nerve regenerates). They are probably caused by ***hypersensitivity of the denervated muscle to the small amount of acetylcholine*** present in the bloodstream according to the **law of denervation** (which states that *denervated structures become hypersensitive to the chemical transmitter that was released by the injured nerve*).

(3) Reaction of degeneration (R.D.) : This is a peculiar change in the ***response of denervated muscles to electric stimuli*** (refer to C.N.S.).

** Other causes of ***muscle atrophy*** include the following :

(a) Damage of the nerve cells from which motor nerves originate (e.g. the anterior horn cells) as occurs in ***poliomyelitis*** (= *infantile paralysis*).

(b) Prolonged muscular inactivity e.g. after prolonged immobilization of a limb as a result of a fracture (= ***disuse atrophy***).

** ***Regeneration of nerves is a very slow process***, thus by the time the injured nerve is regenerated, the paralyzed muscles would have been atrophied. Therefore, it is essential to do therapeutic exercises to these muscles (= ***physiotherapy)*** and also stimulate them electrically at intervals in order to delay their atrophy till the nerve is regenerated .

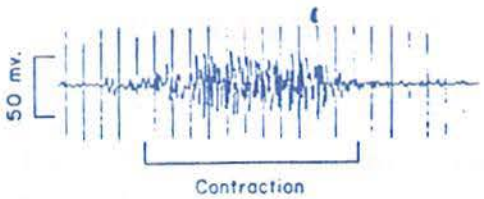


Figure 57 : An electromyogram recorded during muscle contraction.

Muscle fasciculations

These are jerky contractions of groups of muscle fibres due to pathological discharge from spinal motor neurons (= anterior horn cells). They particularly occur ***early in poliomyelitis*** and are ***visible by the naked eye and can also be felt by the patient***.

ELECTROMYOGRAPHY

This is recording of the electrical activity of skeletal muscles on a CRO. The apparatus used is called the ***electromyograph*** and the record obtained is called the ***electromyogram*** (= ***EMG***). 2 types of electrodes can be used :

(1) *Small metal disc electrodes* (placed on the skin overlying the muscle).

(2) *Needle electrodes* [inserted either under the skin (= *hypodermic needle electrodes*) or in the muscle itself]. They can pick up the activity of localized parts of the muscle (or even the activity of single muscle fibres).

During rest, small potentials are recorded (which are caused by the mild contractions of the ***muscle tone***). On activity, more motor units are brought into action producing potentials reaching up to 50 mV (figure 57).

Recording of the EMG is used for ***investigating the activity of skeletal muscles in both health and disease*** e.g. it detects the extent of paralysis in cases of poliomyelitis and after nerve injuries (see above).

** During voluntary movements, the rate of impulse discharge in individual motor units is not rapid, and this tends to produce ***clonic contractions*** (***i.e. incomplete tetanus***). However, the motor units discharge ***asynchronously,*** so the responses of individual muscle fibres merge together and a ***smooth contraction of the whole muscle is produced .***

RIGOR MORTIS

This is stiffening of skeletal muscles that occurs.within 4-5 hours after death. It starts to disappear 12-15 hours later, and complete muscle relaxation occurs after about 25 hours. These time relations are important in ***forensic medicine*** because they help in determination of the time of death.

Cause of rigor mortis

It is a type of ***muscle contracture due to depletion of ATP***. After death, ATP is lost, thus the energy required for active Ca^{2+} re-uptake by the sarcoplasmic reticulum is lost. Thus, the myosin heads remain attached to actin in an abnormal fixed and resistant way leading to muscle rigor. The relaxation of muscles that follows rigor mortis is due to ***autolysis of the muscle proteins by proteolytic enzymes released from the lysosomes*** of dead muscle fibres, and is followed by ***putrefaction due to bacterial action***. Cold storage of dead bodies delays the onset of rigor mortis, but prolongs it once it has occurred.

** There are **another 2 types of muscle rigor (1)** Heat rigor (page 69). **(2)** Calcium rigor in the cardiac muscle (refer to circulation).

THE SMOOTH (PLAIN) MUSCLE

The smooth muscle fibres are ***spindle-shaped non-striated cells*** having long nuclei in the centre, a length of 20-500 microns and a diameter of 2-5 .microns. They are present in the walls of viscera and blood vessels and some glands (e.g. the prostate and seminal vesicles), as well as in the skin (erector pilae muscles), eye (ciliary and pupillary muscles) and subcutaneous tissue (e.g. in the scrotum). Although they do not move the body, yet their function is of great importance because ***they regulate most of the internal vital activities of the body.***

MECHANICAL AND METABOLIC ACTIVITIES

The mechanism of contraction of smooth muscles is almost similar to that of skeletal muscles, since they contain ***thin parallel filaments of actin and myosin*** which slide over each other during contraction. They also contain ***tropomyosin and calmodulin*** (***but no troponin***), and their contraction is activated by Ca^{2+} (which combines to calmodulin). However, in contrast to skeletal muscles, the contraction of smooth muscles is ***involuntary*** (however, the ciliary muscle in the eye can contract voluntarily).

Smooth muscles contain few mitochondria and a poorly-developed sarcoplasmic reticulum as well as the ***energy-producing substances*** found in skeletal muscles (ATP,CP and glycogen). However, they depend to a large degree on ***glycolysis*** for their metabolic needs.

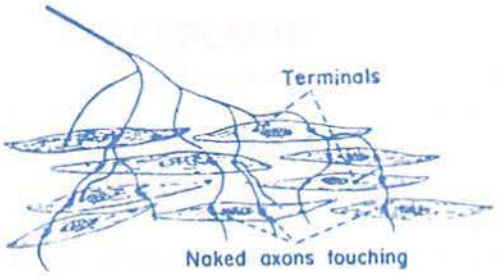


Figure 58 : Innervation (nerve supply) of smooth muscles.

INNERVATION (NERVE SUPPLY)

Smooth muscles receive a double nerve supply from both divisions of the autonomic nervous system (i.e. sympathetic and parasympathetic nerve fibres). These nerves usually exert ***reciprocal actions*** e.g. in the visceral walls, stimulation of the cholinergic (parasympathetic) nerves increases the smooth muscle activity while stimulation of the noradrenergic (sympathetic) nerves decreases it. On the other hand, the reverse occurs in the sphincters of the G.I..T..

The function of these nerves is ***not to initiate smooth muscle contraction but only to modify its inherent activity*** (which is produced by ***an intrinsic myogenic property***). Therefore, if the smooth muscles are denervated, they will not be paralyzed but they continue activity spontaneously (although at a slower rate).

There are ***no motor end plates*** (***M.E.P.***) in smooth muscles. The majority of nerve fibre terminals spread among the smooth muscle fibres, and at the points of contact between them there are special nodes in the nerve (called ***varicosities***) where the neurolemma is deficient, allowing the ***naked axons to contact*** **the** ***muscle fibres directly*** (figure 58). Most neuromuscular transmission in smooth muscles occurs at these varicosities. However, some nerve terminals also release their chemical transmitters among the muscle fibres, which then diffuse in all directions.

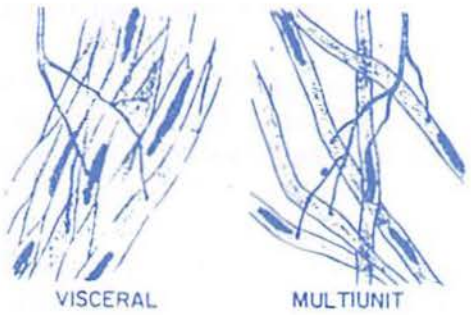


Figure 59 : Types of smooth muscle.

TYPES OF SMOOTH MUSCLE

There are ***2 types of smooth muscle*** (figure 59) **:**

(1) Multiunit smooth muscle : This is made up of discrete (separate) smooth muscle fibres without interconnecting bridges! in between, so it ***does not obey the all or none law***. Generally, this type contracts only when stimulated by nerves producing fine graded contractions, and is mostly found in the iris of the eye and walls of blood vessels.

(2) Single unit (visceral) smooth muscle : This is made up of large sheets of smooth muscle fibres that have low resistance bridges in between forming a ***functional syncytium, so it obeys the all or none law like the*** *cardiac muscle* (page 31) . These bridges are junctions where the membranes of 2 adjacent fibres fuse to form a single membrane. At these areas, the ***permeability to various ions is high and the electric resistance is low*** allowing easy transmission of spike potentials form one muscle fibre to the other. Accordingly, when one of these fibres is stimulated the impulse is rapidly conducted to the surrounding fibres. This type is found in the walls of hollow viscera (e.g. the intestine, uterus and ureters).

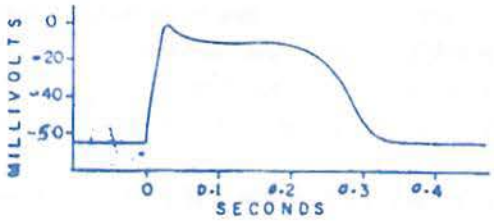


Figure 60 : An action potential recorded from a smooth muscle fibre showing prolonged plateau during repolarization.

PROPERTIES OF VISCERAL SMOOTH MUSCLE

(1) It is *much less excitable than skeletal muscles*. Its contraction is sluggish and its ***chronaxie is much longer***, and the process of excitation-contraction coupling is very slow. However, like the cardiac muscle, it contracts ***as one unit*** because it forms a ***functional syncytium that obeys the all or none law*** (page 31).

(2) It is sensitive to changes in pH, osmotic pressure, temperature, drugs, chemicals and hormones (because it is continuously exposed to the changes that occur in the ***internal environment*** of the body).

(3) Its O_2 consumption is about 1/4 that of skeletal muscles, so it is ***not rapidly fatigued***.

(4) Electric activity : The resting membrane potential of visceral smooth muscle is ***unstable***. It is relatively low when the tissue is active and higher when it is inhibited. It averages ***-50 mV in periods of relative rest***. The following waves superimpose on the resting membrane potential

a- ***Slow sine wave-like fluctuations*** few mV in magnitude with spikes (i.e. AP) superimposing on their rising or falling phases. These spikes sometimes overshoot the zero potential line and in some tissues, the produced action potentials have a ***prolonged plateau*** during repolarization as that recorded in cardiac muscle (figure 60).

b- ***Pacemaker potentials*** (= prepotentials) similar to those recorded from, the S.A. node of the heart (refer to circulation).

(5) Tone (tonus) : Visceral muscle shows continuous irregular contractions (independent of its nerve supply) that cause a maintained state of partial contraction known as tone (or tonus). These contractions are produced by the ***repetitive discharge of spike potentials*** (see above).

(6) Rhythmicity : Visceral muscle also shows regular rhythmic contractions in addition to the maintained tonus (figure 61) which are initiated by the ***pacemaker potentials*** (see above). These potentials are generated from special ***self-excitable muscle fibres*** at regular intervals (so they are the ***pace maker of rhythmicity, like the S.A. node of the heart***).

It is to be noted that the ***tonus and rhythmicity are not related*** e.g. an increase in the strength of the tonus may be accompanied by a simultaneous decrease of the amplitude of the rhythmic contractions (figure 61).

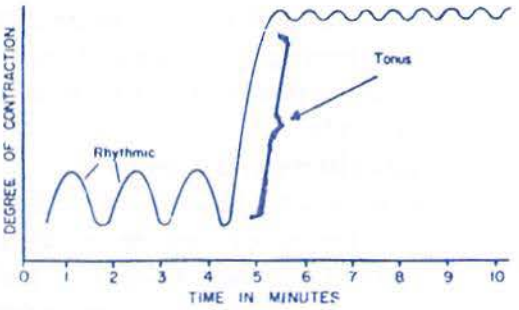


Figure 61 : A record of tonus & rhythmic contractions in smooth muscles.

(7) Plasticity (relation of length to tension) : If a piece of visceral muscle is slowly stretched, the developed tension is high at first, but if the stretch is maintained (i.e. the muscle is held at the greater length) the tension gradually decreases (sometimes below the initial level) and the new length is maintained. This is called the property of plasticity, and it allows ***the hollow viscera to accomodate large amounts of contents without much increase in pressure*** e.g. the stomach on receiving large amounts of food and the urinary bladder on receiving large volumes of urine.

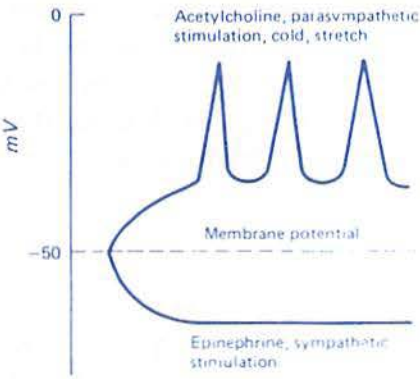


Figure 62 : Effects of various agents on the membrane potential and excitability of the intestinal smooth muscle.

Factors that affect smooth muscle excitability

(1) Ions : Excess Ca^{2+} decreases the excitability of smooth muscle while excess K^{+} increases it (opposite to their effects in cardiac muscle).

(2) pH : Excess acidity decreases while excess alkalinity increases the smooth muscle excitability.

(3) Osmotic pressure : Hypertonic solutions decrease while hypotonic solutions increase the smooth muscle excitability.

(4) Temperature : Cold increases the smooth muscle excitability. It decreases the membrane potential and increases the frequency of spike potentials (figure 62).

(5) Stretch : Rapid stretch of smooth muscle (in absence of extrinsic nerves) increases its excitability leading to its contraction. Stretch is followed by a decline in the membrane potential and an increase in the frequency of spike potentials (figure 62).

(6) Autonomic neurotransmitters and drugs :

a- Acetylcholine (or parasympathetic stimulation) and parasympathomimetic drugs (page 27) increase the smooth muscle excitability leading to its contraction by a mechanism similar to that of cold & stretch (figure 62).

b- Norepinephrine (or sympathetic stimulation), epinephrine and other sympathomimetic drugs (page 17), and parasympatholytic drugs (e.g. atropine) decrease the smooth muscle excitability leading to its relaxation. by a mechanism opposite to that of cold and stretch (figure 62).

(7) Hormones ::

a- ***Catecholamines decrease the smooth muscle exditability*** (see above).

b- ***Vasopressin*** (= *a hormone released by the posterior pituitary gland*) ***increases the smooth muscle excitability*** (similar to acetylcholine).

c- The ovarian hormones (***estrogen and progesterone***) exert specific effects on the excitability of smooth muscle in the wall of the uterus (figure 63). ***Estrogen increases the excitability of the uterine smooth muscle*** and accordingly its tonus increases and spontaneous contractions occur (although it increases rather than decreases the membrane potential). On the other hand, progesterone decreases the excitability of the uterine smooth muscle leading to its relaxation (because it markedly increases the membrane potential and inhibits the discharge of spike potentials).

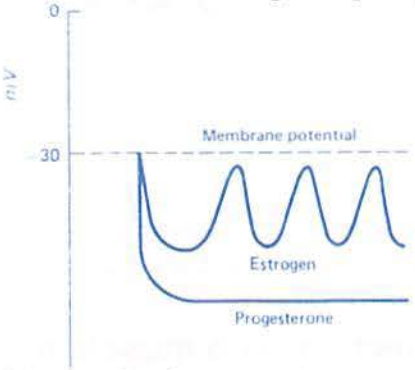


Figure 63 : Effects of the ovarian hormones (estrogen and progesterone) on the membrane potential and excitability of the uterine smooth muscle.

McArdle's disease (myo-phosphorylase deficiency glycogenosis)

This disease is characterized by ***congenital deficiency of the muscle phosphorylase enzyme***. This leads to ***accumulation of glycogen in the skeletal muscles***, and the patients complain ***muscle pain and stiffness on performing exercise***. In addition, their ***exercise tolerance is markedly decreased*** because the muscle glycogen is not broken down to provide the energy required for muscle contraction.

TRANSPORT OF SUBSTANCES THROUGH CELL MEMBRANES

THE CELL MEMBRANE

This is a very thin elastic semipermeable membrane that surrounds the cell. Its thickness is 75-100 A°(A° = Angstrom = 0.1 millimicron = 0.1 nm) and underlying most cells, there is also a thin fuzzy layer and some fibrils which make up a ***basement membrane***.

Chemically, the cell membrane is composed primarily of proteins (55 %), lipids (42 %), together with a small amount of carbohydrates (3 %) combined almost entirely to proteins forming glycoproteins.

The basic structure of the cell membrane is a ***lipid bilayer***, embedded in which in a random way large globular protein molecules (figure 64). The major lipids are ***phospholipid molecules***, the shape of which is similar to a ***clothespin***. The head of the molecule contains the phosphate portion and is quite soluble in water (= ***hydrophilic***), while its tail is insoluble in water (= ***hydrophobic***). The hydrophilic heads are exposed to the aqueous environments that bath the exterior and interior of the cells, while the hydrophobic tails meet in the water-poor interior part of the membrane.

The proteins in cell membranes are 2 kinds **(a)** ***Integral proteins*** (which extend all the way through the cell membrane) **(b)** ***Peripheral proteins*** (which are only attached to the outer and inner surfaces of the cell membrane, but they do not penetrate it). **Functionally, these proteins are**

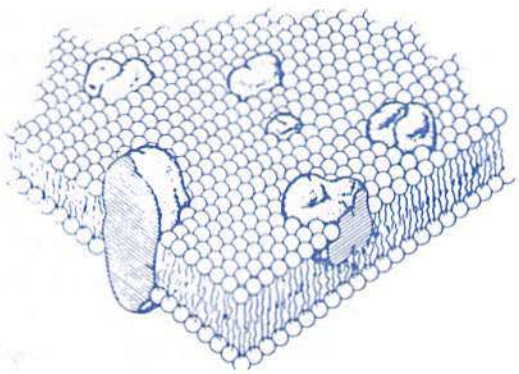


Figure 64 : Structure of the cell membrane. Notice the lipid bilayer and the clothespin shape of the phospholipid molecules. Proteins are shown as irregular shaded globules.

classified into the following 7 types :

(1) ***Structural proteins*** **:** Some of these contain lipids (lipoproteins) while others contain carbohydrates (glycoproteins).

(2) ***Pumps*** **:** These actively transport ions across the cell membranes.

(3) ***Receptors :*** These bind neurotransmitters and hormones, which initiates physiological changes inside the cell.

(4) ***Carriers*** : These transport various substances down their electro-chemical gradients by ***facilitated diffusion*** (see later).

(5) ***Antibody processing*** by specific glycoproteins that also distinguish self from nonself (refer to blood, chapter 7).

(6) ***Enzymes*** (***particularly the peripheral proteins***) : These catalyze chemical reactions at the surface of the cell membrane.

(7) ***Ion channels*** (***particularly the integral proteins***) : These permit passage of various ions into or out of the cell.

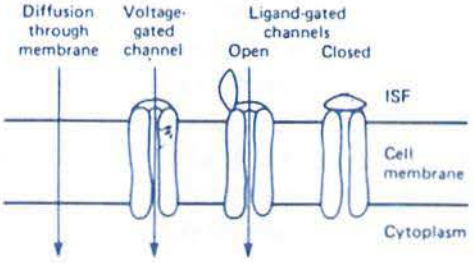


Figure 65 : Diffusion pathways. ISF = Interstitial fluid.

TRANSPORT MECHAMSMS ACROSS CELL MEMBRANES

(1) DIFFUSION

This is a passive process (i.e. requiring no energy) by means of which a substance in solution (or in a gas) expands to occupy all of the available volume. It is produced by the ***kinetic motion of the molecules*** (which makes them in a continuous ***random movement***), and it occurs in the direction of their ***concentration*** (= ***chemical***) ***or electrical gradients*** i.e. from areas of high concentration to areas of lower concentration.

In the body, substances diffuse not only within the same compartment but also through cell membranes. This occurs through either the lipid bilayer or the proteins embedded in it, depending on the ***molecular size, lipid solubility and charge of the substance***. Generally, diffusion across cell membranes can be divided into 2 main types : **simple diffusion and facilitated diffusion**.

(1) Simple diffusion

This occurs through the ***lipid bilayer*** as well as through channels present between certain transport proteins in the cell membrane called the ***channel proteins*** (so these channels are known as the ***protein channels***).

(a) Simple diffusion through the lipid bilayer

The following substances can easily diffuse through the lipid bilayer :

(1) Lipid-soluble substances (e.g. O_2, N_2 and alcohol) **:** These substances dissolve in the lipid bilayer, so they cross the cell membranes easily.

(2) Water **:** The lipid bilayer is permeable to water (although water is insoluble in lipids) because water molecules are small and have high kinetic energy that allows their penetration like bullets through the lipid bilayer.

(3) *Small* uncharged water-soluble molecules e.g. CO_2 (which is also lipid soluble). *Large* uncharged water-soluble molecules (e.g. glucose) and the charged particles (i.e. *ions*) diffuse much slowly by this route.

(b) Simple diffusion through protein channels

This is specially important for ***diffusion of ions and the large water-soluble molecules***.

Protein channels are highly selective e.g. there are specific channels for transport of Na^+, K^+ and Ca^{2+} (called Na^+, K^+ & Ca^{2+} channels). Some channels are continuously open (= ***leak channels***) while most of them are gated i.e. they have gates that open or close (figure 65). These are either **:**

(1) Voltage-gated i.e. open or close by alterations in the membrane potential e.g. the fast and slow channels (page 40).

(2) Ligand-gated i.e. open or close by binding to a ligand. Ligands are often extracellular (e.g. neurotransmitters and hormones) but they can also be intracellular (e.g. Ca^{2+}, cyclic AMP or one of the G proteins).

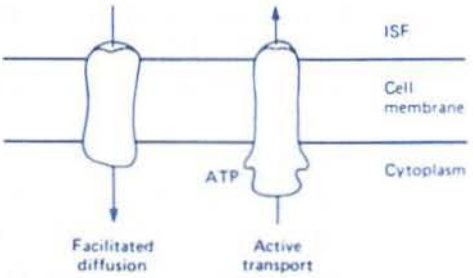


Figure 66 : Facilitated diffusion and active transport (using carrier proteins in the cell membrane). ISF = Interstitial fluid.

(2) Facilitated diffusion

This mechanism of diffusion also moves substances ***passively*** in the direction of their ***chemical or electrical gradients***, *but it requires transport proteins* called ***carrier proteins*** (so it is also called ***carrier-mediated diffusion***). The molecules of substances that diffuse by this mechanism (e.g. glucose and amino acids) bind to one of the carrier proteins. This causes conformational change in the protein which leads to movement of the bound molecule from one side of the cell to the other i.e. the ***carrier protein facilitates diffusion of the substance to the other side*** (figure 66).

In many sites, facilitated diffusion is ***regulated by hormones*** e.g. insulin can increase the rate of glucose diffusion into the cells 10- 20 fold.

FACTORS THAT AFFECT THE RATE OF DIFFUSION

(1) Permeability of the membrane : The greater the permeability of the membrane, the more will be the rate of diffusion, and vice versa. Such permeability is influenced by the following factors :

(a) ***Thickness of the membrane*** : The greater the thickness, the lesser will be the rate of diffusion, and vice versa.

(b) ***Lipid solubility*** **:** The greater the solubility of the substance in lipids, the greater the amount that dissolves in the cell membranes and the more will be the rate of diffusion, and vice versa.

(c) ***Number of protein channels*** **:** The rate of diffusion is directly related to the number of these channels per unit area.

(d) ***Temperature*** **:** Heat increases the motion of molecules, so diffusion increases directly in proportion to increase of temperature.

(e) ***Molecular weight of diffusing substances*** **:** The smaller the molecular size, the greater will be the rate of diffusion, and vice versa.

(2) Surface area of **the membrane :** The larger the surface area of the membrane (e.g. that of a capillary), the greater will be the total rate of diffusion, and vice versa.

(3) Concentration difference (= concentration or chemical gradient) : The larger the difference in concentration of the substance on both sides of the membrane, the greater will be the rate of its diffusion from the higher to the lower concentration side, and vice versa.

(4) Electrical potential : This particularly affects the rate of diffusion of ions. Whenever there is a. difference in potential between 2 compartments, the positive ions move along an electrical gradient to the more negative compartment while negative ions move in the opposite direction.

(5) Pressure difference (= pressure gradient) : The larger the difference in pressure of the fluids on both sides of the membrane (e.g. that of a capillary), the greater will be the rate of diffusion from the higher to the lower pressure side, and vice versa.

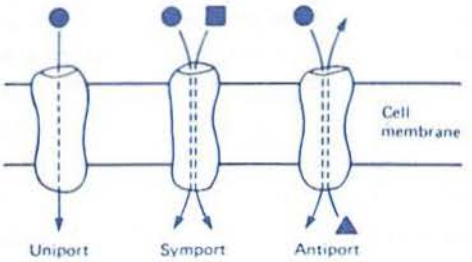


Figure 67 : Types of carrier (transport) proteins in cell membranes.

(2) ACTIVE TRANSPORT

This is the transport of substances ***against their electrical or concentration gradients*** (i.e. from a lesser to a greater concentration). It requires ***specific carrier proteins as well as energy***. The latter is provided mainly by ***hydrolysis of ATP*** (therefore, the carrier molecules are mostly ATPase enzymes that catalyze the hydrolysis of ATP). A typical example of active transport is the transport of Na^+ and K^+ across the membranes of muscle and nerve fibres by the Na^+- K^+ pump (refer to nerve and muscle).

** Both ***facilitated diffusion and active transport are carrier-mediated transport mechanisms***. However, active transport requires energy and occurs against concentration and electrical gradients. while facilitated diffusion does not require energy and occurs only along concentration and electrical gradients

There are ***3 types of carrier proteins*** (figure 67) which are the following :

(1) Uniports : These transport only one substance.

(2) Symports : These transport 2 substances simultaneously in the ***same direction*** (= ***co-transport***).

(3) Antiports : These transport 2 substances simultaneously but in ***opposite directions*** (= ***counter-transport***).

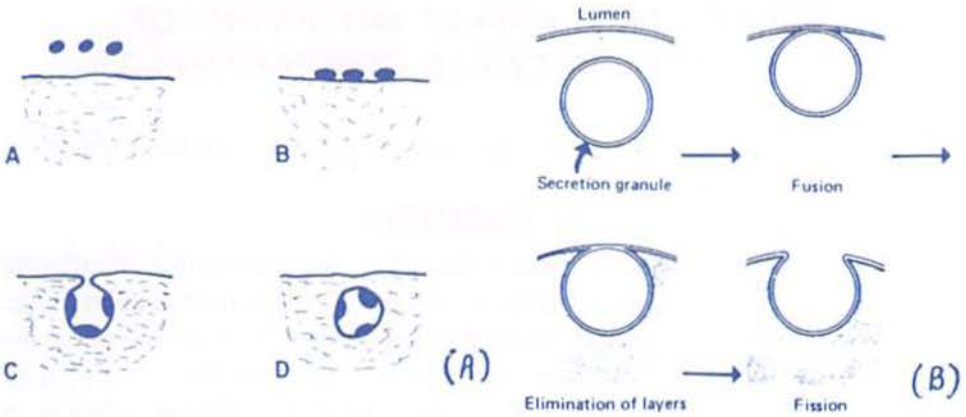


Figure 68 : Mechanism of pinocytosis (A) and exocytosis (B).

Pinocytosis (= cell drinking)

This is a transport mechanism by means of which large particles (e.g. proteins) cross cell membranes and enter the cells (when simple diffusion, facilitated diffusion and active transport cannot occur).

The particle first contacts the cell membrane (figure 68 A). Then, the latter is depressed (making an invagination into the cell) and on each side it rises and folds over the particle (which will become a vacuole inside the cytoplasm the wall of which is made of a part of the cell membrane).

Phagocytosis (= cell eating)

This is a process by means of which bacteria and dead tissue are engulfed by cells, and it is essentially the ***same as pinocytosis*** except that in the latter the ingested substances are in solution.

Both pinocytosis and phagocytosis are called ***endocytosis***, and they are ***active processes*** since they are markedly decreased when the energy producing processes in the cell are blocked. There are **2 kinds of endocytosis**:

(a) ***Constitutive endocytosis*** **:** This is a continuous process that is not induced by ligands.

(b) ***Receptor-mediated endocytosis*** **:** This is triggered by ligands that bind to receptors on the cell surface, and it occurs via special coated pits on the cell membranes.

Exocytosis (= cell vomiting)

This is the ***reverse of endocytosis***. It is also an active process (since it (requires energy and Ca^{2+}) by means of which secretory granules (or vesicles) are extruded out of the cell. The membrane of the granule or vesicle fuses with the cell membrane, then the area of fusion breaks down and its contents are expelled outside the cell while the cell membrane remains intact (figure 68 B), but the mechanism of breakdown is unknown.

FORCES THAT AFFECT MOVEMENT OF SUBSTANCES BETWEEN COMPARTMENTS

The movement of water and other molecules across cell membranes is affected by the following forces **:**

(1) OSMOSIS

This is the ***movement of water*** through a semipermeable membrane from an area containing pure water or a diluted solution of a solute (e.g. NaCl or glucose) to an area in which there is a higher concentration of this solute (figure 69). The pressure required to apply on the concentrated solution so as to prevent water movement from the diluted solution is called the ***osmotic pressure***.

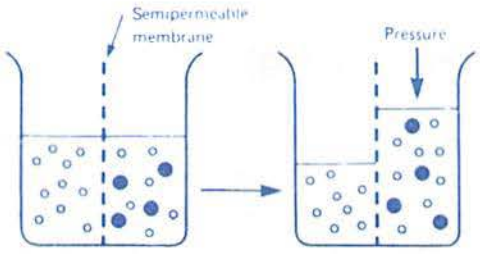


Figure 69 : Diagrammatic representation of osmosis. The open circles represent water molecules while the solid circles represent solute molecules.

The amount of osmotic pressure is ***directly proportional to the number of particles per unit volume of solution***. So, ionizing solutes (e.g. NaCl) are more osmotically active (because each ion is active by itself) than non-ionizable solutes (e.g. glucose).

The osmotic pressure is expressed in ***osmoles or milliosmoles*** (which can be converted to mmHg (***one milliosmole =1 / 1000 osmole = 19.3 mm Hg***). All body fluids have the same osmolality (about ***290 milliosmoles per litre*** = about ***5500 mmHg*** = about ***7.3 atmospheric pressure***).

Solutions that have an osmolality equal to that of the plasma are called ***isotonic solutions***, while those having a higher osmolality are ***hypertonic***, and those having a lower osmolality are ***hypotonic***.

** A ***0.9 % NaCl solution and a 5 % glucose solution are both isotonic***. However, in the latter condition *glucose is metabolized in the body, and the net effect will be that of a hypotonic solution.*

(2) FILTRATION AND ULTRA-FILTRATION

Filtration is a process by means of which a fluid (with its dissolved molecules) is forced through a porous membrane due to a ***difference in hydrostatic pressure on the 2 sides*** of the membrane. The amount of the filtered fluid per unit time is directly proportional to the ***difference in pressure, the surface area of the membrane and its permeability***. An example of filtration is the ***formation of the interstitial*** (= ***tissue***) ***fluid through the capillary membranes*** (refer to circulation).

Ultrafiltration means more fine filtration. It separates colloids suspended in crystalloid solutions and also the particles of different sizes in a colloid mixture. An example of ultrafiltration is the formation of the ***glomerular filtrate in Bowman's capsules of the nephrons*** (refer to kidney).

(3) DONNAN'S EFFECT

This effect occurs when 2 ionizable compounds are separated by a permeable membrane but one of the compounds contains a non-diffusible ion. The diffusible ions will pass freely through the membrane till their ***products on the 2 sides become equal*** as follows (diagrammatically) :

X	membrane	Y
K^+		K^+
Cl^-		Cl^-
Protein		

X and Y are 2 compartments separated by a membrane which is ***impermeable to protein*** but freely permeable to both K^+ and Cl^-. Suppose that the concentration of all anions and that of K^+ on one side of the membrane are initially equal to their concentrations on the other side. Accordingly, Cl^- tends to diffuse down its concentration gradient from Y to X, and some K^+ move with it to maintain electrical neutrality on side Y. This process continues till an quilibrium is established as follows :

$\frac{[K^+] \text{ in X}}{[K^+] \text{ in Y}} = \frac{[Cl^-] \text{ in Y}}{[Cl^-] \text{ in X}}$ i. e. $[K^+]$ in X . $[Cl^-]$ in X = $[K^+]$ in Y . $[Cl^-]$ in Y

This is known as the **Gibbs-Donnan equation**. The Donnan's effect on the distribution of diffusible ions is important in the body because of the presence of large amounts of non-diffusible protein anions in the cells and plasma. Examples of the Donnan's effect in the body are the ***chloride shift phenomenon*** in the red blood cells (refer to respiration) and the ***differences in ionic concentration between the plasma and the glomerular filtrate*** (refer to kidney).

(4) DIALYSIS

This is a process by means of which particles having high molecular weights (= *macromolecules*) can be separated from small molecules and ions. As shown in figure 70, a mixture of protein and NaCl is placed in container (B) and is separated from pure water kept in vessel (A) by a semipermeable cellophane tubing.

The osmotic pressure of the mixture forces water to pass from (A) to (B). At the same time, NaCl passes from (B) to (A) by its concentration gradient, and by frequent changing of water in (A), the mixture in (B) can be made free from NaCl.

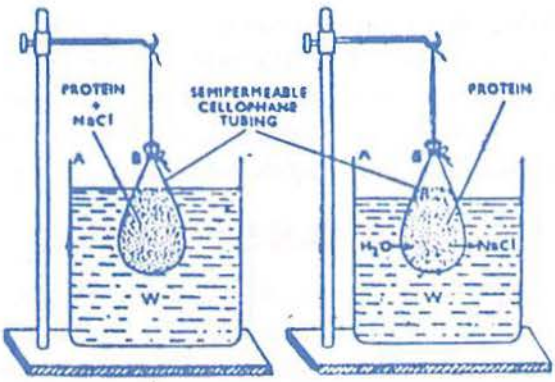


Figure 70 : Dialysis. W = water.

(5) SOLVENT DRAG

When a solvent is moving in one direction by ***bulk flow***, it tends to drag (= take) some molecules of solute with it. This force is called solvent drag and is normally ***a negligible force*** because in most situations in the body its effects are very small.

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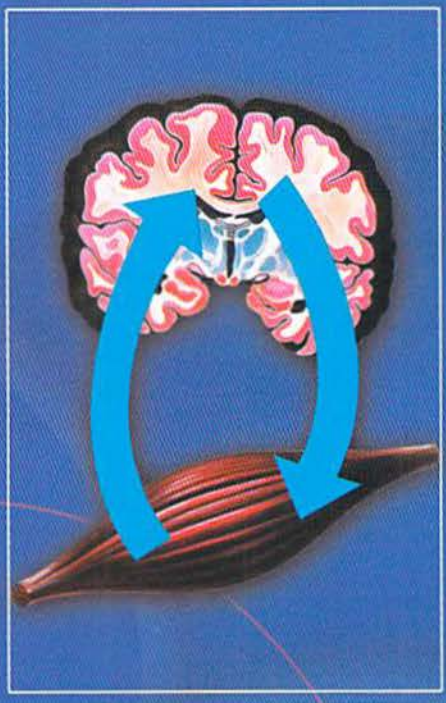

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